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The Arthur E. Mills Memorial Oration.[1]

ROOSEVELT AND HOPKINS.

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THE responsibility rests upon the President and Council of The Royal Australasian College of Physicians for choosing me as the person who is to have the honour of delivering this the third Arthur E. Mills Memorial Oration. For the confidence in me which the choice implies I desire to express my very grateful surprise. But it is a misguided choice. I am not qualified to put forward ideas or sentiments which would form a worthy memorial of the remarkable man in remembrance of whom we are gathered in this hall.

I am not, however, under the necessity of attempting so difficult a thing. For it has been left to me to choose the subject. I have used this privilege in a manner which I hope is not inappropriate to the occasion. I have decided to speak of two very great men, of each of whom I think it may be truly said that his work and his character cannot properly be understood by anyone who is unmindful of his medical history. It was my great good fortune to meet Mr. Roosevelt and Mr. Harry Hopkins on not a few occasions during the War and of both of them I have borne away a very vivid personal impression which has been confirmed by all that I have read since.

These famous men exerted their highest influence upon the course of history in a crowded period of time commencing almost at the very date when the life we are met to commemorate came to a close.

Professor Arthur Edward Mills died on April 10, 1940, a month to a day before the German onslaught on Holland, Belgium and France began. He saw the destruction of Poland and those intolerable first seven months of suspense before the invasion of Norway, when the War was so woefully misinterpreted in many quarters, particularly in the United States. It was before the outbreak of the Kaiser's war that he had become a lecturer in the principles and practice of medicine in the University of Sydney and had laid the foundation of his reputation as a teacher. But it was in the dozen years after the War that as a professor his influence became most powerful. It is not for a mere lawyer to attempt to analyse the qualities of a great exponent of the art and science of medicine who left such a lasting impression upon his contemporaries and his students. That is to be done by someone who knew him and who now stands in the same tradition. It is the occasion, not the discourse, that commemorates the life and

[1] Delivered at the annual meeting of The Royal Australasian College of Physicians, Hobart, March 20, 1953.

the work of Arthur Edward Mills. The discourse is but a votive offered to his memory.

In the second chapter of the volume called "The Grand Alliance" Mr. Churchill writes:

> On January 10 a gentleman arrived to see me at Downing Street with the highest credentials. Telegrams had been received from Washington stating that he was the closest confidant and personal agent of the President. I therefore arranged that . . . we should lunch together alone the next day. Thus I met Harry Hopkins, that extraordinary man, who played, and was to play, a sometimes decisive part in the whole movement of the war. His was a soul that flamed out of a frail and failing body. He was a crumbling lighthouse from which there shone the beams that led great fleets to harbour. He had also a gift of sardonic humour. I always enjoyed his company, especially when things went ill. He could also be very disagreeable and say hard and sour things. My experiences were teaching me to be able to do this too, if need be. At our first meeting we were about three hours together, and I soon comprehended his personal dynamism and the outstanding importance of his mission. This was the height of the London bombing, and many local worries imposed themselves upon us. But it was evident to me that here was an envoy from the President of supreme importance to our life. . . . Everyone who came in contact with Harry Hopkins in the long struggle will confirm what I have set down about his remarkable personality. And from this hour began a friendship between us which sailed serenely over all earthquakes and convulsions. He was the most faithful and perfect channel of communication between the President and me. But far more than that, he was for several years the main prop and animator of Roosevelt himself. Together these two men, the one a subordinate without public office, the other commanding the mighty Republic, were capable of taking decisions of the highest consequence over the whole area of the English-speaking world.

Yet this same man was hated bitterly by a great many of his own countrymen. It was a widely held view that at best he was an ill-balanced unpractical visionary exercising nothing but an evil influence upon Roosevelt. What will be the judgement of history? "Histories", said Carlyle, "are as perfect as the historian is wise and is gifted with an eye and a soul." If ever these rare qualities are combined in an English historian of the future, he will confirm the verdict of Mr. Churchill. And yet he will be puzzled at the possession by so great a mind of commonplace and unrefined tastes and interests, usually enjoyed by an intelligence of a lower level. If he is an American historian he will indeed need a steady eye and soaring soul to overcome his own political prejudices and those of the sources which he consults. In England for a long period Clio was a Whig, but in the United States she inspires now a Democratic, now a Republican version of history. A British estimate of Harry Hopkins will not suffer from these prejudices. Our difficulty is of another kind. You will have noticed that Mr. Churchill describes him as "a subordinate without public office". The institutions of democratic government with which alone most of us are familiar are British. How, we ask, could a man without public office and at best a subordinate be "the prop and animator of the President" and "play a decisive part in the whole movement of the war"? The system of government which makes such a thing possible is quite unlike ours. It is one in which the supreme executive power of the State is vested in one man, the President, and at the same time is divorced entirely from the legislative power that is vested in Congress. The President's ministers of State hold office at his pleasure and neither he nor they are responsible to Congress. The President may appoint whom he likes to public office and, though, in the case of some of the older high offices, the appointment must be approved by the Senate, it is always open to him to employ whom he likes upon specific tasks and to take counsel with whom he pleases. You will recall that Mr. Woodrow Wilson in foreign affairs placed great reliance on his friend Colonel House, who always declined public office. President Wilson entrusted to him diplomatic missions of the gravest consequence. But the analogy between the two cases is imperfect. House was no Hopkins. It was found possible to describe House as the Talleyrand from Texas. But the enmity to Hopkins was not expressed in satire of this form. His fidelity to the President was never in doubt and he held the President's confidence so completely that, when he represented the President, it was felt that he spoke as his *alter ego*.

There was little in his upbringing or in his early experience which would have been considered a preparation for these great responsibilities. He was born at Sioux City in the State of Iowa in the year 1890. His father was a harness maker and storekeeper, and his mother, before her marriage, had been a school mistress. In his boyhood he was desperately ill with typhoid fever. His schooling was of a routine description. From school he went to college at Grinnell, in his native State, whence he graduated in 1912. It is appropriate to the present occasion to speak of the importance of the contribution a professor's influence may make in the future work of a student destined to a position of power. It happened that one professor whom Harry Hopkins admired had spent a considerable time in England, had become a friend of James Bryce, had mixed with the group forming the Fabian Society and had studied British institutions. Was this the cause of his receptive use of the economics of the New Deal and of his ready understanding of the considerations governing British policy and action in war? At Grinnell College there was too a professor, named Dr. Edward A. Steiner, who had lived in Russia and had known Tolstoy. He is said greatly to have influenced the future envoy whom Roosevelt was to send to Moscow immediately after Hitler's invasion of Russia. It was this teacher who was responsible for starting Harry Hopkins upon the work which he made his vocation. His vocation was indeed unexpected for a man bred up in the cornbelt, and it formed a strange preparation for a statesmanship in war. It was that of a welfare worker in the slums of New York. At the instance of Dr. Steiner he went from Grinnell to a summer camp for poor children conducted by a charitable institution at work in the east side of New York. What he saw was a revelation to him and he became zealous in social work and ardent in social reform. He joined the staff of the institution as a worker in the slums, his recompense being his subsistence and a nominal salary. It is not my purpose to trace the career he made for himself in his chosen field. I mention it only to explain the man and because it was the occasion of his forming such close relations with Roosevelt. It is enough to say that he passed into the service of the important and well supported Association for the Improvement of the Conditions of the Poor, that he was appointed Executive Secretary of the Board of Child Welfare of New York, and that he was rejected in 1917 by the Armed Forces for war service and joined the Red Cross by which body he was sent to direct the Gulf Division from New Orleans. In 1921 he rejoined the Association for the Improvement of the Conditions of the Poor, this time in the Health Division, whence in 1924 he was appointed Executive Director of the New York Tuberculosis Association, a position he held for seven years. When in 1929 Roosevelt became Governor of the State of New York, Harry Hopkins was well known as a most successful director of the Tuberculosis Association.

He actually met Roosevelt for the first time during the election campaign, but it was after the Governor had taken office that Harry Hopkins was brought much under his notice and then it was done by Mrs. Roosevelt, whose interest in welfare work was always strong, and by her husband's friends. The backgrounds of the two men could hardly have differed more widely. The upbringing and education of Mr. Roosevelt was that of an American gentleman. He was born some eight years before Harry Hopkins at Hyde Park, above the Hudson River, where his father had established himself as a country gentleman after retiring from business in New York. In his turn the son made the mansion at Hyde Park his home and his use of it, first as Governor and then as President, has given it almost a place in history. The Roosevelts are a very old New York family. Politically the family falls into two branches, a Republican branch and a Democratic branch. To the former branch belonged Theodore Roosevelt, Republican President from the assassination of McKinley in 1901 until Taft succeeded him in 1909. Franklin Delano

Roosevelt was his fifth cousin. Franklin's school was Groton, the exclusive New England school of which an American has said with more bitterness than penetration that it is more English than Eton and Harrow. When Theodore was a candidate for the Vice-Presidency in 1900 Franklin was at Harvard and in the true tradition of the Democratic branch he opposed the candidacy of his Republican cousin. But the families were not divided. Elliott, Theodore's younger brother, was godfather to Franklin Delano. Eleanor, Elliott's daughter, and Franklin met as boy and girl and before Franklin had actually graduated from Harvard the marriage between this famous pair took place. It was less than a fortnight after Theodore's inauguration for his second term as President. He took part in the ceremony and gave the bride away. This led to an enormous concourse of people who came to see the President and blocked the street. It was in March, 1905. When in 1913 Harry Hopkins married it was to a humble fellow welfare worker in the charity he served.

The conditions and experience of his early life may have been responsible for the liberal and radical politics of Hopkins. But that could not be said of Franklin Roosevelt. His political opinions and tendencies were certainly not the product of hardship. Certainly they were not the product of study or of philosophical speculation. Perhaps they were no more than a family inheritance. But on most problems of their times he and Hopkins seemed to share much the same outlook. Roosevelt had yet to study law. This he did at the Columbia Law School. He was admitted to the New York Bar in 1907 and joined a firm of attorneys with whom he practised for three years. Then in 1910 he turned to a political career. He was then twenty-eight years of age. He was persuaded to seek the Democratic nomination for a seat in the New York State Senate, a seat not very easy to win. In an energetic personal canvass among the country folk he seems to have displayed some of the charm and friendliness which in later years he appeared to be able to exert, not only over people who saw him, but also over the multitudes who only heard his voice over the radio. His pictures of that time accord with the descriptions of those who knew him. They show a tall, thin, but athletic-looking young man of refined appearance. His features were regular and clear cut. His complexion was fair. His blue eyes were set deep. Apparently he appealed to the farmers; for they elected him, though a Democrat. But once in the State Senate he made but little impression upon his colleagues and associates, who perhaps smacked too much of New York machine politics. At this time, apparently, he did anything but expose himself to the accusation so frequently heard later; the accusation that he seemed prepared to enlist as supporters, if not as confidants, men whose political technique hardly accorded with the ethical standard set at Groton and Harvard. The Tammany Democrats thought he was arrogant.

Roosevelt's next step in his political advancement was to accept the post of Assistant Secretary for the Navy. Mr. Woodrow Wilson became President on March 4, 1913, and Josephus Daniels became his Secretary for the Navy. Roosevelt had brought himself under their notice at the Democratic Convention of 1912 by the part he took in securing Mr. Wilson's nomination, and the invitation to become Assistant Secretary was perhaps the consequence. It was thus that Roosevelt came to Washington. He had always been interested in the Navy. He had desired when he was a boy to make it his career. He served under Josephus Daniels until, at the end of Mr. Woodrow Wilson's second term, he was nominated as the Democratic candidate for the Vice-Presidency at the elections in which the Democrats were so overwhelmingly defeated and Warren Harding was chosen President. To my mind it is one of the notable facts of history that Mr. Roosevelt held the post of Assistant Secretary for the Navy during this period. He was young and virile. He knew England and Germany. He formed part of an administration which first strove desperately to preserve neutrality and in the end felt forced by Germany's contemptuous disregard of America's rights as a neutral to seek a declaration of war from Congress. He learned at close quarters the meaning of sea power and he saw that America did not possess it. He witnessed the collapse of Germany, the announcement by his President of the Fourteen Points and their acceptance by Germany, and he knew that at Versailles a treaty had been framed which departed from the fourteen points. He saw the Senate reject the treaty, but not for that reason, and he saw them reject the covenant of the League of Nations. He saw America shrink from the assumption of her full responsibilities as a powerful member of the society of nations and at the same time submit herself to the sordid régime of Harding. The lessons he then learned from these things can be seen again and again in the very different course his policy took from the very outbreak of war in Europe until, with the end in sight, the United Nations Organization was planned at Dumbarton Oaks and the unconditional surrender of Germany grew imminent as he died.

When Harding entered the White House as President on March 4, 1921, Roosevelt ceased to hold any office or employment. Five months later came the tremendous crisis of his life. He was upon a holiday at an island of New Brunswick called Campobello where he and his family sometimes went. Suddenly he became ill with poliomyelitis. The story of his illness has been told in the books that have appeared since his death. In due time he learned that his lower limbs were incurably paralysed. For a time his upper limbs seemed affected, but he regained full use of them. I will not recount the history of his illness and convalescence. It is a story of fortitude, courage and determination. He persevered in adjusting himself to his crippled condition. His discovery of Warm Springs meant much to him, and he expended part of his fortune in setting it up as a resort for sufferers from poliomyelitis. His own patience and the strengthening of his spirit had its counterpart in the devotion of his wife and the development of her character. Mr. Wendell Wilkie took the view that the qualities which Mr. Roosevelt's misfortune had called forth and the conditions of life that it imposed had, indeed, been a source of strength: they had contributed to the President's great success. He pointed out that Mr. Roosevelt had been a tall, vigorous and animated figure, who, like other men, must have consumed much of his time and energy in going hither and thither and complying with the conventional requirements imposed upon those prominent in public life. Not only was he saved from this, but, in the long period of his convalescence, he had time for reading and reflection. His secretariat could protect him from unprofitable visits. His work, of necessity, was at his desk, and there, it may be assumed, his reliance on documents increased and he mastered them more thoroughly.

It was nearly seven years after the onset of his illness that he reentered politics. Al Smith was Governor of New York and he had been nominated by the Democratic Convention as their candidate for the Presidency of the United States. Al Smith found that powerful elements in his own State had turned away from him and he conceived the idea that Mr. Roosevelt, who had appeared at the convention and made a speech nominating him, could pull round the State if he would only run for the governorship. He appealed to Mrs. Roosevelt, but she said "it was absolutely impossible". Again and again he telephoned to Mr. Roosevelt. The answer of the latter was that he was not well enough. It was out of the question. But at length he began to weaken and asked that his wife should take the telephone. "Do you think carrying New York depends on my running for Governor?" he asked his wife. "I am afraid it does", she said. "They think I have an obligation to run. What do you think?" "I know it's hard", she answered, "but that is what they believe." He then gave in. Upon the decision so given his reentry into public life depended. Perhaps if it had not been for this simple conversation between husband and wife he would never have been President of the United States. He fought the campaign himself. He improvised means of overcoming his physical diability. He demonstrated to himself that he was not too weak or too incapacitated to play a man's part. But it must have required great courage and involved

much humiliation. It was thus that he attained the governorship of the State of New York. He then knew, he must have known, that his ascendancy over his bodily condition was now complete.

When early in his term as Governor Harry Hopkins came under his notice in the way I have described, the United States was on the threshold of the great financial depression. As it developed it fell to the Governor to deal with the unemployment and destitution that followed. Roosevelt set up in the State of New York an organization, the Temporary Emergency Relief Administration. Of this Hopkins became executive director under a chairman whom, very soon, he succeeded. Conditions worsened and it was not long before a million people had sought emergency relief from his administration. His association with the Governor grew closer as the problem of relief loomed larger and larger. At the Democratic Convention of 1932 Roosevelt was nominated as the Democratic candidate for the Presidency and he was elected at the poll in November of that year. At that time the inauguration still took place on March 4 of the year following the election. Here is a description which long afterwards Roosevelt gave of the state of affairs confronting him:

> Those who lived through the months immediately preceding March, 1933, do not require a description of the desperate condition into which the American economy had fallen since the crash of 1929 . . . By Inauguration Day the banks of the United States were all closed, financial transactions had ceased, business and industry had sunk to their lowest levels. The widespread unemployment which accompanied the collapse had created a genuine feeling of utter helplessness. I sought principally . . . to banish, so far as possible, the fear of the present and of the future which held the American people and the American spirit in its grasp.

Roosevelt had no doubt of the necessity of taking Harry Hopkins with him to Washington and Hopkins had no doubt about the necessity of his going. The measures, direct and economic, which Roosevelt's administration took by way of relief are a matter of history and it is not my purpose to describe them. It was Hopkins who administered them. He became the Administrator of Federal Emergency Relief at once. He presided over the Public Works Administration and the Civil Works Administration. Then in 1935 he was appointed Works Progress Administrator. In this period the policies of Roosevelt, of which Harry Hopkins's administration formed no small part, doubtless gave American life and thought a new direction. They were the cause of deep division of opinion throughout America. Roosevelt and Hopkins became the centre of acute controversies and the objects of bitter animosities.

In the summer of the year 1937 Hopkins, whose second wife had recently died of cancer, suspected that he too was a victim. He went into the Mayo Clinic, where his suspicions were confirmed. The greater part of his stomach was removed. He remained in the Mayo Clinic for the rest of the year and after that there was a further period of convalescence.

Roosevelt, before he decided upon the unprecedented course of seeking a third term as President, had planned to secure the democratic nomination of 1940 for Harry Hopkins. This plan he persisted in for some time notwithstanding Hopkins's illness. When he was well enough Roosevelt appointed him Secretary of Commerce, a post he held until August, 1940. What are described as nutritional disorders incapacitated him for the greater part of this period, no inconsiderable part of which he spent in the Mayo Clinic. When he died it was of hæmochromatosis. In May, 1940, however, he entered the White House to reside with Roosevelt and there he remained. In the three or four years that followed he played a great part in the allied conduct of the War. He made many journeys to many distant places and bore the strain of much hard work. His importance in the counsels of the Allies cannot be overstated. Field Marshal Sir John Dill, whose own place in the history of the War is assured, wrote to him in February, 1944: "I know of no one who has done more by wise and courageous advice to advance our common cause." He had broken down almost finally on New Year's Day, 1944, and was in the Mayo Clinic, where he had undergone another severe operation. He had now made his effective contribution to the War, but throughout his dependence on medical aid had been almost constant. At a very early stage he seemed to renounce all the aspirations which Roosevelt's plans for him had aroused. Ambition, self-interest, ostentation, or a desire for fame appeared in none of his work. He spared no exertion and no sacrifice. To describe his work would involve a narration of the higher Allied direction of the War. The purposes he served were many. His remarkable gift for reducing a great and complicated problem to its essentials, combined as it was with exceptional shrewdness and a penetrating, though composed, and restrained judgement made Roosevelt feel that his guidance was at once safe and indispensable. He possessed the confidence of the Chiefs of Staff of both countries and supported them. In the great work of the Munitions Assignment Boards, which allocated armaments, his authority was paramount. In spite of his state of health he was the President's trusted emissary who won the confidence of the British Prime Minister and Chiefs of Staff.

In the White House he often endeavoured to analyse the problems arising for the President's decision before they reached him and to find the solution. As you will know, one of the great difficulties in 1942, and later, was to maintain, while the Allies built up their strength, a proper balance between the necessities of the War in the Pacific and the demands made by the strategy which concentrated upon Germany as the enemy which must be defeated first. I remember at the end of August, 1942, spending an hour with Harry Hopkins in his bedroom at the White House when he went over the whole picture with a simple and clear mastery. He knew what Australia had said on the subject in her communications to the President. He was anxious that her views should not be answered hastily or unsympathetically and, so far as he was concerned, he was quite ready to fly out to Australia. But the picture to him consisted of the facts and to his mind the most important facts were the present and future availability of arms and men and their disposition in the various theatres of war. Some days later he renewed the subject and, had not Roosevelt intervened, I believe that Hopkins would have come to Australia simply to do his best to see that the Australian Government was fully informed and was satisfied. But next day Mr. Roosevelt, in the course of a long discussion of the same difficulties, said: "You have been trying to get Harry Hopkins out to your country", a statement which did not do full justice to Hopkins's readiness to go. "Well", said the President, "I am not going to let him go. He is not fit for such a journey. Besides I need him here." The President went on to say why and for what purpose.

The last time I saw Harry Hopkins was in September, 1944. The War was in a very different state then. He had spent the greater part of the year in hospital and he spoke of the opportunity it had given him for reflection. He had had no documents and he said that lying in hospital he had thought much about the War in the Pacific, concerning which he was not without ideas. He wished us to take a conspicuous part in what was to come and thought it important for our prestige in the post-war world that we should do so. But he himself was sadly changed. He had always been a slight figure; but his alert mind, his firm intelligence and his lucid though animated exposition left you without any feeling that he was handicapped by his health. That was no longer so.

By that time, too, Mr. Roosevelt's physical appearance had changed very much. It is the picture of him as he had been that I should like to give you. I had the good fortune, which I believe fell to few Australians, of seeing Mr. Roosevelt on many occasions and conversing with him. It was only because I held the office of Australian Minister in Washington that I saw Mr. Roosevelt. The time of my first seeing him was when the War was at its most difficult stage for Australia, and, I think, at its most difficult stage for America. It was due to the state of the War and the difficulties to which the situation gave rise that I was fortunate enough to see the President so often. But,

though this was so, he seemed always to treat you as an individual. The first and indeed the most permanent impression that you received was the astonishing courage with which he overcame his affliction. I was a member of a small body over which he presided. We met in the cabinet room. Mr. Roosevelt was wheeled in by a coloured attendant. It is not easy to forget the picture. His cheerful smile: the characteristic motion of his hand holding a cigarette in a long holder and waving us to our seats: the cheerful words of greeting. From his wheeled chair, he was able with the strength of his arms to transfer himself to the swivel chair at the end of the table. When I first saw him he had been living without the effective use of his lower limbs for twenty-one years. In this time he had been President of the United States for ten years and, before that, Governor of New York for four years. Has any man, ever, so triumphed over physical disabilities? His mode of life was, of course, regulated by his disability. His exercise was swimming. Thought had obviously been given to the arrangements by which he could have within reach what he was likely to need. It is the tradition at the White House for the President to attend, at times, to affairs of state in his private apartments. In Mr. Roosevelt's room upstairs his desk was placed across a corner. He sat in the angle upon a swivel chair. Behind him on the walls was stretched a series of linen pockets to hold maps, papers and the like, all within his reach. The desk was covered with gadgets and knick-knacks. Small tables at either side carried other things. When he was in his office downstairs, his aides and secretaries were at hand and he relied more upon them for anything he needed. But when he had lunch in his office, as he not infrequently did, a hot canteen was brought to his side and from it he appeared to prefer to serve himself and you if he had summoned you to lunch with him for the purpose of discussion. The cabinet room was close to his office. But under the form of government of the United States, cabinets have not the same significance as they have with us. Their purpose is different. Great affairs of state are settled more often than not by the President personally, after, it is to be hoped, consultation with the Minister concerned. The White House contained other personal advisers of the President as well as Harry Hopkins. Perhaps it is not fanciful to suppose that this was in part because of his disability and the dependence on others it entailed. For years Mr. Roosevelt bore fearful responsibilities: he sustained the weight of unremitting work, and he endured the continual strain of political controversy and personal attack. Yet his vivacity of temperament could not but strike you. It is a quality that he retained in spite of all the difficulties that encompassed him. His liveliness of mind was combined with a good humour which was not easily disturbed. I have seen him very grave. I have seen him angered, but only when the occasion for gravity was deep or for anger potent and acute. His self-control always seemed complete and it is difficult to believe that he ever allowed himself to lose his self-possession or composure. His sense of fun was considerable and was constantly asserting itself. He liked to enliven the gravest affairs with amusing illustrations. He would employ anecdote, but rather of the present than of the past. If he told, for example, what had passed at a conference, he left no doubt that the characteristic oddities of the parties to it, however eminent, had not escaped him. Mr. Roosevelt was by no means artless in giving rein to his sense of fun. He knew as well as any man how useful it might prove in relieving a situation or preventing one arising. But at times he seemed to be moved by simple enjoyment of an incident and to speak without art or design. I remember his coming into a meeting consisting of half a dozen or so of us and beginning with an account —quite irrelevant to our business—of the misfortunes of a journalist, a journalist whom in the past he had considered troublesome. It appeared that the journalist had gone as a war correspondent to a front that happened to be under a British command. There he had got into trouble with the Army authorities and had been placed under detention by the British command. Mr. Roosevelt recounted the incident and said: "I always believed the British Commander [naming him] was a great general, but now I am sure of it." Of his interest in people I think there can be little doubt. That, too, perhaps developed after his illness. But his friendliness was, I think, felt by many people as something more than good-humoured pleasantness. It was easy for him to deal with people and he believed thoroughly in the importance of personal contact. He valued first-hand information obtained from people whom he saw. Always he appeared to me to speak about things that had occurred with a freedom I should not have expected. Even in the darker days of the War his mind seemed to turn to the future, to the shape things were to take after victory. He was essentially forward looking and he did not appear to doubt that his health and strength would carry him into the post-war period. But of Mr. Churchill's health he expressed misgivings. "He will kill himself", he said. "He spends every waking hour of his life in the most intense concentration upon the War. He never thinks of anything else." And then he compared his own case: the enforced distractions which the administration of the domestic affairs of America provided, and his own ability to find occasional relief or respite in some simple interest. But his own vitality was ebbing. His appearance showed that. No one who has studied the published pictures of the meeting at Yalta between him and Stalin can fail to see that it was an *impar congressus*. It is not difficult to understand why that is treated by so many as the beginning of a course of successful manœuvres on the part of the Soviet by which our leaders were outwitted. Harry Hopkins journeyed to Yalta, but was too ill to take any part or be of any real assistance to Roosevelt. It is true that he survived the President. He did not die until January 29, 1946. But his effective life was spent.

Mr. Roosevelt died on April 12, 1945. On April 30 Hitler committed suicide. On May 7, at General Eisenhower's headquarters, Field Marshal Jodl signed the instrument of surrender. On May 23 Mr. Winston Churchill resigned office as Prime Minister of the Coalition Government. These events marked the end of one phase and the opening of a new phase of this epoch of mutation and conflict. Two weeks before his death Mr. Roosevelt had informed at least one of his Cabinet that the war in Europe would end in May. He died in the hour of victory knowing that victory was at hand. Perhaps there was "no hour so fit". He had seen Mr. Woodrow Wilson die a broken man, his hopes shattered and the plans which other countries had accepted from his hands rejected by his own country. Mr. Roosevelt was at least spared that. His own health was already broken and it is difficult to suppose that he could have sustained the burdens of his office amid the stresses, strains and anxieties of the years that have since passed. His work was done. But this, I believe, was a fact that he did not realize. His mind looked ever forward. The war to him was an episode in an unfolding drama: an unexpected episode, but one to be followed by a *dénouement;* and the *dénouement* might make it possible to reconstruct the world so that ever after the life of ordinary men might be happy. It has been the grand illusion of great men that by reconstruction the world may be made a place for the unimpeded pursuit of happiness. How grotesque Mr. Roosevelt's illusion was, if he really entertained it, we, the survivors, are acutely aware.

But we ought not to weigh this too heavily against his achievements. If you look back over the 177 years of the history of America as a nation you will find a multitude of famous names. You will find no President who so dominated the contemporary scene. You will find none so devoted to the advancement of his country and none with such a certain faith in her high destiny. The part he played in the tremendous events of his time and the contribution made by Hopkins must be assessed by history. All that I have endeavoured to do is to sketch the development of the two men and to indicate, though faintly, the kind of personality they each displayed and to show you why, independently of the assessment that history may make of their work in the government of the affairs of men, what each accomplished in face of what he suffered forms a magnificent human achievement exhibiting the qualities of true greatness.

THE TREATMENT OF CHRONIC RHEUMATISM WITH "BUTAZOLIDIN".

By MICHAEL KELLY,
Melbourne.

FOUR years ago a new compound called "Irgapyrin" was first used in European rheumatic clinics. The reports of its usefulness (Belart, 1949; Wilhelmi, 1950; Pulver, 1950; Gsell and Müller, 1950; Loewenhardt, 1950; Fähndrich and Junkersdorf, 1950; Kienle, 1950; Fischer, 1951; Fabre and Mach, 1951) did not arouse much interest, because it was claimed simply to be injectible amidopyrine.

Amidopyrine is almost insoluble in water, but it is absorbed from the alimentary tract and is rapidly broken down and excreted (Pulver, 1950). Since 1884 it has been known as a mild analgesic like aspirin, with slight effects on rheumatic pain. But it occasionally causes fatal neutropenia.

When antirheumatic effects were claimed for "Irgapyrin", it was suggested that the blood level of amidopyrine when it was injected must have been unusually high. But Currie (1952) found that the level was the same in rheumatic patients treated with "Irgapyrin" (who alone claimed relief of pain) as in those treated with amidopyrine. Therefore he investigated the new substance, supposedly inert, which the pharmaceutical firm of Geigy had synthesized merely as a solvent for amidopyrine.

This is a white powder, insoluble in water, known as phenylbutazone or "Butazolidin", a pyrazolidine derivative related to amidopyrin (Figure I). It is mildly analgesic to animals (Wilhelmi, 1949); in the body it is slowly broken down and excreted (Pulver, 1950).

At the European Rheumatology Congress in Barcelona, Currie (1951) reported that injections of "Butazolidin" had relieved the pain of 14 patients with fibrositis. More recently, 77 out of 81 patients with acute exacerbations of rheumatoid arthritis claimed substantial relief (Currie, 1952); in 24 there was objective evidence of improvement (reduction of joint swelling, greater range of movement, greater strength of muscles). Kuzell *et alii* (1952) and Brown and Currie (1952) reported that "Butazolidin" was equally effective by mouth; they have been supported by many recent writers (Hart and Johnson, 1952*a*; Bach, 1952; Slot, 1952; Gillhespy, 1952; Hogarth, 1952; Loxton *et alii*, 1952; Shulman, 1952; Davies *et alii*, 1952; Stephens *et alii*, 1952; Steinbrocker *et alii*, 1952; Plichet, 1952; Patterson *et alii*, 1953; Cudkowics and Jacobs, 1953; Selbourne, 1953).

"Butazolidin" in Practice.

Fifty-five patients with rheumatic disorders have had 74 courses of treatment (Table I); 38 had continuous treatment for at least six weeks, and 13 of these (because of early shortage of supplies) had previously had shorter courses of one or two weeks. In Column 7 I have tried to measure the relief by taking the residual pain as a percentage of the original pain. In cases of rheumatism the patient complains of pain, and he assesses treatment in terms of relief of pain. The objective signs—stiffness and swelling—are secondary to the pain, and their assessment is often difficult. The patient is the only witness we have, and if we question him carefully we can get valuable information from him.

Five patients (Cases XXI, XXII, XXXVI, XLVII, L) are excluded from this assessment because the temporary improvement could have been due to other causes. In the remaining 50, pain has been substantially relieved by 63 out of 70 courses of treatment. The patient feels better within twelve hours and usually improves for two days. With the relief of pain the joints feel freer and there is often a sense of well-being, less pronounced than the euphoria which cortisone brings on. Often the patient is tempted to activity which has been beyond his powers, and this may cause a recurrence of the pain (Cases VII, XXVI, XXIX, XXXIV, XL, LIII, LV).

In every case (except Case XV) in which the patient had been relieved during a short course, the pains returned to their original intensity within forty-eight hours of the substitution of other tablets for "Butazolidin". In a few cases the pains were worse than before for a week or two; but this withdrawal reaction is not as severe as that which follows cortisone.

Osteoarthritis.

Osteoarthritis of the hip has been consistently relieved in striking fashion (Cases I to IX). The patient usually says that the joint feels much freer, and its range has often been objectively increased. In several cases the limp has vanished.

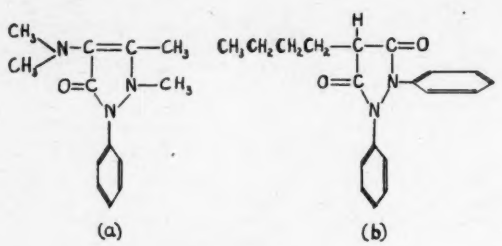

FIGURE I.

Osteoarthritis of other joints has also been relieved. In Case X, painful swelling of the knees twice subsided within two days of commencement of treatment.

Multiple Fibrositis.

In several patients with multiple pains the relief was even more spectacular than in those with osteoarthritis. Two (Cases XIV and XV) were almost completely relieved during a short course; the pain recurred when "Butazolidin" became unavailable, only to disappear again on a second course of treatment. In Cases XXI and XXII complications caused discontinuance within a few days; and the temporary improvement is not claimed to be due to the drug, because the patients' symptoms had fluctuated from day to day for years.

Localized Fibrositis.

Several patients with localized pain have been dramatically relieved, but the proportion of failures has been greater. When the pain has been purely muscular the results have been better than when nerve roots have been involved (Cases XXXI, XXXII, XXXIV). One patient (Case XXVIII) was relieved of pain in the knee in two earlier courses, but failed to secure relief when the drug finally became available in quantity.

Periarthritis of the Shoulder.

In four cases of periarthritis of the shoulder relief was dramatic, while in one (Case XXXVI) with mental depression, treatment was discontinued after a week because conclusive data could not be secured. In Case XXXIX a second course of treatment was not so successful as the first course.

Rheumatoid Arthritis.

All the patients with rheumatoid arthritis—except in Case XLIV—improved with "Butazolidin", but the relief was less spectacular, and in some it was not lasting. In Cases XLVII and L the data are inconclusive because other methods of treatment were applied at the same time. In Case LII a second course with high dosage failed to relieve, though an earlier short course had given great relief.

In Cases XLIII, LIII, LIV (exacerbation of a single joint in an old rheumatoid condition), improvement was dramatic and the swelling subsided in a few days. In other patients the swelling of joints was reduced more gradually.

TABLE I.

Case Number, Patient.	Sex, Age (Years.)	Clinical Details.	Duration of Disease. (Years.)	Daily Dose.[1]	Duration of Treatment. (Weeks.)	Residual Pain. (Percentage.)[2]	Complications.	Remarks.[3]
		Osteoarthritis: Seventeen Courses of Treatment in Thirteen Patients.						
I N.D.	F., 53	Painful arthritis of hip; Paget's disease of ilium. Emotional.	2	1·2	1	30 (100)	Yes.	D.(C.).
II H.M.D.	F., 73	Arthritis of left hip and both wrists; pain greater than limitation.	5	1·2	1	30 (70)	Yes.	D.(S.). Pain returned to 70%.
III, E.P.K.	M., 69	Pain and gross limitation of both hips.	5	(*a*) 0·6 (*b*) 0·6	2 4	30 (100) 40	—	D.(S.). D.(F.).
IV, H.J.H.	F., 78	Severe pains and deformity of right hip; bed. Post-fracture necrosis of femoral head (nailed). Emotional.	2	0·6	1	20 (100)	—	D.(S.).
V, T.E.C.	M., 59	Medium pain and limitation of both hips. Chauffeur.	4	(*a*) 0·6 (*b*) 0·6	1 20	30 (100) 30	—	T. Limp vanished.
VI, T.F.M.	M., 62	Arthritis of left hip after osteomyelitis of femoral neck. Confined to house for six months.	10	(*a*) 0·6 (*b*) 0·8	1 20	40 (100) 30	—	T. Loss of energy.
VII, H.R.	F., 67	Severe deformity and pain of both hips. Can only shuffle along.	6	0·6	19	20 to 40	—	T. Too much walking.
VIII, H.L.B.	M., 63	Medium pain and limitation of right hip.	1	0·6	16	20	Yes.	D.(C.). Limp vanished.
IX, C.F.L.	M., 63	Gross limitation and pain of both hips.	8	0·6	15	10	Yes.	D.(C.).
X, E.L.	F., 67	Pain and swelling of knees, right more than left, after injury to right.	8/12	(*a*) 0·6 (*b*) 0·8	1 8	20 (100) 0	No. Yes.	D.(R.). Swelling of knee vanished each time.
XI, J.E.G.	F., 60	Pain and swelling of knees, right more than left.	3	0·6	6	0	Yes.	D.(R.).
XII, A.H.M.	M., 48	Pain in both elbows on using hands. Full range.	3	0·6	4	50	—	T.
XIII, U.I.T.	F., 55	Pain and swelling of four proximal interphalangeal joints, after injury.	2	0·6	4	100	—	T.
		Multiple Fibrositis: Twelve Courses in Ten Patients.						
XIV, E.F.H.	F., 42	Muscular pains all over. No swelling of joints. Obesity.	1	(*a*) 0·6 (*b*) 0·6	2 22	10 (80) 0	—	T.
XV, D.E.C.	F., 42	Pain in back and knees, worse on movement.	4/12	(*a*) 0·6 (*b*) 0·6	2 20	0 (50) 0	Yes.	T. Pain returned to 50% of previous intensity.
XVI, E.A.E.	M., 51	Severe pain and stiffness of neck, shoulders, dorsal and lumbar spine.	1	0·8	24	30	Yes.	T. Stiffness reduced 50%.
XVII, J.J.F.	M., 50	Generalized pains. No swelling of joints. Emotional.	3	0·8	8	30	—	T.
XVIII, H.T.	F., 47	Persistent pains in back and limbs. No limitation of movements.	5	0·6	1	30 (100)	Yes.	D.(C.). Allergic to many drugs.
XIX, C.V.B.	F., 63	Pains in back 13 years, shoulders three years, knees two years, with some limitation but no swelling.	13	0·6	17	20	—	T.
XX, S.M.I.	F., 31	Pains in left shoulder, right hip, feet, right wrist. Previous rheumatic history.	4/12	0·6	3	10	—	T. Range of shoulder increased rapidly.
XXI, F.M.G.	F., 37	Persistent pains in arms, legs and back: non-articular, began after scarlatina, cortisone did not relieve. Emotional.	8	0·8	1	50 (100)	Yes.	D.(C.). Pains fluctuate daily. A severe illness.
XXII, A.B.	F., 53	Persistent pains in arms and legs. Began after measles. Emotional.	5	0·6	1	50 (100)	Yes.	D.(S.). Pains fluctuate daily.
XXIII, K.A.H.	F., 30	Pains in hands and feet without swelling. Cortisone did not relieve.	6/12	0·8	1	100	—	D.(F.).
		Localized Fibrositis: Fourteen Courses in Eleven Patients.						
XXIV, A.T.	M., 19	Pain in back of chest.	2	0·6	1	100	—	D.(F.).
XXV, O.H.	M., 65	Pain in shoulder on abduction. Full range.	8/12	0·6	3	10	Yes.	D.(C.).
XXVI R.S.	M., 58	Lumbar backache—worst on movement; after prostatectomy.	2	0·6	4	20 to 50	—	T. Too much activity.
XXVII, P.O.D.	M., 69	Pain in left gluteus on stooping.	1	0·6	2	20	—	T.

[1] (*a*), (*b*), (*c*) = separate courses of treatment.

[2] Figure shows percentage of original pain; figure in parentheses is percentage when course discontinued.

[3] D.(C.) = treatment discontinued because of complications. D.(S.) = treatment discontinued because of shortage of drug. D.(F.) = treatment discontinued because of failure to relieve pain. D.(R.) = treatment discontinued because patient relieved. T. = patient still under treatment.

TABLE I.—*Continued.*

Case Number, Patient.	Sex, Age (Years.)	Clinical Details.	Duration of Disease. (Years.)	Daily Dose.[1]	Duration of Treatment. (Weeks.)	Residual Pain. (Percentage.)[2]	Complications.	Remarks.[3]
XXVIII, R.B.	F., 71	Severe pain in right knee: local lipomatosis. Full range; X-ray findings negative.	2	(*a*) 1·2 (*b*) 0·6 (*c*) 1·0	1 1 3	20 (100) 30 (100) 100	—	D.(F.).
XXIX, E.A.R.	M., 50	Pain on rotating neck: X-ray findings negative.	1	0·6	5	20 to 60	Yes.	T. Too much activity.
XXX, J.A.A.	F., 22	Residual pains after neuritis of left lower brachial plexus.	8/12	0·6	3	10	Yes.	T. Loss of energy.
XXXI, V.C.C.	M., 54	Left sciatic neuritis. Foot numb.	1	0·6	4	40	—	T.
XXXII, E.C.L.	M., 54	Severe left sciatic pain.	4/12	1·0	2	50 to 100	—	D.(F.).
XXXIII, S.F.C.	F., 57	Radicular pain in neck and arms after injury.	6	0·6	1	100	—	D.(F.).
XXXIV,	M., 49	Severe left sciatic pain three months, after generalized pains nine months. Lost 50 pounds.	9/12	(*a*) 0·6 (*b*) 0·6, 1·0	1 6	40 (100) 30 to 80	—	D.(F.). Carcinoma of pancreas.
		Periarthritis of Shoulder: Six Courses in Five Patients.						
XXXV, E.C.	F., 46	Pain and stiffness of shoulders; loss of weight. Pains here and there.	3	0·6	20	20	Yes.	T. Stiffness of shoulders much reduced.
XXXVI, E.D.	M., 52	Severe limitation and pain, left greater than right. Diabetes.	2	0·6	1	100	—	D.(S.). Data inconclusive; very depressed.
XXXVII, L.J.P.	M., 64	Severe pains in shoulders alternately. No fixation.	3/12	0·6	4	10	Yes.	D.(C.).
XXXVIII, R.D.T.	F., 48	Pain in shoulders (right greater than left); range of right reduced 50%.	3	0·6	10	10	—	T.
XXXIX, H.L.	F., 54	Severe pain in right shoulder; no voluntary movement, but not fixed. Backache for 15 years. Emotional.	2/12	(*a*) 0·6 (*b*) 0·6, 0·8	1 10	10 (100) 20 to 40	—	T.
		Rheumatoid Arthritis: Twenty-five Courses in Sixteen Patients.						
XL, M.C.T.	F., 49	Painful swelling of hands, feet and wrists. Stiffness of shoulders; painful knees. Followed bronchitis.	3	(*a*) 1·2 (*b*) 0·6 (*c*) 0·6	2 3 10	40 (100) 50 (100) 50	Yes. No. Yes.	D.(F.). Swelling of most joints reduced. Too much activity.
XLI, M.M.C.	F., 46	Intermittent swelling of hands and wrists; painful nocturnal attacks. Bronchiectasis. Emotional disturbances.	1	(*a*) 1·2 (*b*) 0·6 (*c*) 0·6	1 1 16	30 (100) 40 (100) 50	Yes. Yes. Yes.	T. Sputum reduced during treatment.
XLII, A.K.S.	F., 49	Swelling and deformity of hands, knees and wrists. Stiff shoulders.	8	0·6	1	50 (100)	—	D.(S.).
XLIII, G.A.M.	M., 64	Pain, stiffness, swelling of feet and hands; painful shoulders. Acute exacerbation of right knee.	3	(*a*) 0·6 (*b*) 0·6	2 20	30 (100) 0	No. Yes.	T. Swelling of knee subsided rapidly.
XLIV, R.T.	F., 40	Pains and swelling of hands and feet, stiff shoulders.	2	0·6, 1·0	2	100	—	D.(F.).
XLV, E.C.T.	F., 62	Pain and swelling of hands, feet and knees; stiff shoulders. Using crutches. Emotional disturbances.	3	(*a*) 0·6 (*b*) 0·8	1 20	50 30	—	T.
XLVI, M.M.R.	F., 25	Pain and swelling of hands, feet and right knee.	4	(*a*) 0·6 (*b*) 0·8	1 20	50 (100) 50	Yes. Yes.	T.
XLVII, E.K.	F., 42	Painful stiffness and swelling of fingers and toes.	6	0·6	2	50	—	D.(S.). Other treatments.
XLVIII, N.J.S.	F., 51	Intermittent painful swelling of many joints and continuous of left ankle.	3	0·6	21	0	—	T. Swelling of ankle subsided rapidly; mild rash on face.
XLIX, H.W.B.	F., 59	Deformity of fingers and toes for 22 years; subsided, but painful swelling recurred.	3	0·6	5	40	Yes.	T.
L, J.H.C.	M., 24	Many joints acutely involved; cortisone continuously for three months.	6/12	0·8	20	50	—	T. Other treatments.
LI, C.J.A.	M., 31	Chronic swelling and deformity of hands, elbows and feet. Stiff neck and shoulders. Recent general pains.	22	0·6	21	30	—	T. Bowels free for a few days.
LII, M.B.B.	F., 54	Old arthritis which settled down but left deformities of hands and feet. Recurrences of pains in shoulders, hands and back.	2	(*a*) 0·6 (*b*) 0·6, 1·0	1 4	20 (100) 40 to 100	— Yes.	D.(F.C.).
LIII, W.J.A.	M., 51	Chronic swelling of wrists, hands, feet and stiff shoulders. Flare up in knees, two months.	15	(*a*) 0·6 (*b*) 0·8	20 20	30 20	—	T. Swelling of knees subsided rapidly.
LIV, J.B.M.	M., 24	Swelling of knees and elbows. Flare up in left elbow, three months. Previous rheumatic history.	3	0·6	8	20	—	T. Swelling of elbow subsided rapidly.
LV, M.E.P.	F., 60	Painful swelling of wrists and ankles for two years. Stiff left shoulder.	2	0·6	18	20	—	T. Too much activity caused return of pain.

[1] (*a*), (*b*), (*c*) = separate courses of treatment.

[2] Figure shows percentage of original pain; figure in parentheses is percentage when course discontinued.

[3] D.(C.) = treatment discontinued because of complications. D.(S.) = treatment discontinued because of shortage of drug. D.(F.) = treatment discontinued because of failure to relieve pain. D.(R.) = treatment discontinued because patient relieved. T. = patient still under treatment.

Dosage.

At the beginning the daily dose recommended was 1·2 grammes; the incidence of complications was high (Cases I, II, XXVIII, XL, XLI). For some time after this I used a commencing dose of 0·6 or 0·8 gramme per day (Table I). In a later series of 100 cases, however, I have seldom exceeded 0·4 gramme per day. When this dose fails, a higher one is not likely to succeed. Steinbrocker (1953) supports this observation. Often this dose can be reduced later to 0·2 gramme per day, and occasionally it may be tapered off to nothing.

If the pain recurs while the patient is under treatment, the "Butazolidin" should be interrupted for a week or two, and then resumed. The response of the body is

TABLE II.

Complications of "Butazolidin" Treatment of 55 Patients.

Case Number.	Dose.[1] (Grammes.)	Complications.[2]
I	1·2	Epigastric pain, collapse, visual hallucinations. Treatment discontinued.
II	1·2	Epigastric pain. Treatment discontinued (shortage).
X	0·8	Mild dyspepsia; slight œdema of legs. Subsided.
XI	0·6	Rash; loss of energy. Subsided.
XV	0·6	Ulceration of mouth. Healed.
XVI	0·8	Slight nausea. Subsided when dose reduced.
XVIII	0·6	Headache, epigastric pain, numbness of face. Treatment discontinued temporarily.
XXI	0·6	Headache, nausea, swelling of right leg. Treatment discontinued (failure).
XXII	0·6	Headache, rash, erythema, œdema. Treatment discontinued (shortage).
XXV	0·6	Nausea. Treatment temporarily interrupted.
XXIX	0·6	Dyspepsia, melæna from hæmorrhoids. Treatment continued.
XXX	0·6	Swelling of left eyelid and right hand. Subsided. Loss of energy.
XXXV	0·6	Epigastric pain, swelling of legs. Subsided.
XL	(*a*) 1·2	Dyspepsia; melæna from hæmorrhoids.
	(*c*) 0·6	Dyspepsia. Subsided.
XLI	(*a*) 1·2	Epigastric pain, swelling of legs. Treatment interrupted.
	(*b*) 0·6	Mild swelling of legs.
	(*c*) 0·6	Mild swelling of legs. Treatment continued.
XLIII	(*b*) 0·6	Mild swelling of legs. Treatment continued.
XLVI	(*a*) 0·6	Puffy eyelids; epigastric pain. Treatment discontinued (shortage).
	(*b*) 0·8	Puffy eyelids, epigastric discomfort. Treatment continued.
XLIX	0·6	Nausea; subsided. Then stomatitis, rash. Treatment interrupted.
LII	(*b*) 0·6	Nausea, vomiting, weakness. Treatment discontinued (failure).

[1] (*a*), (*b*), (*c*) = separate courses of treatment.

[2] More recently, severe dyspepsia occurred in cases VIII, IX and XXXVII, and a transient rash in Case XLVIII.

phasic; if it does not respond today it may next week. Treatment should not be abandoned until three four-day trials (the last with 0·6 gramme per day) have failed.

At present I am investigating the suggestion of Lawrence (1953) that the effective dose is 0·4 gramme at a time, given only when symptoms demand it.

Complications.

Table II shows that 23 out of 55 patients complained of nausea, epigastric pain, œdema of legs or elsewhere, maculo-papular eruptions or central nervous symptoms of various kinds. In only 11 cases was treatment interrupted, and in all except one it was resumed again.

After further experience of 260 patients, however, I now prefer to interrupt treatment when symptoms appear and resume it again when they have gone. The onset of complications is unpredictable; they are nearly as frequent with a dosage of 0·4 gramme per day as with higher doses. Dyspepsia is the only side-effect which is especially liable to recur in patients who have already had it and recovered.

Gastric symptoms have occurred in 15% of the patients; sometimes they are severe, and the patient is very miserable. Gastro-intestinal hæmorrhages have been reported by many (Kuzell *et alii*; Hart and Johnson, 1952*b*; Stephens *et alii*, 1952; Granirer, 1952; Ross and Baldwin, 1953; Cudkowics and Jacobs, 1953) with one death (Medico-Legal, 1952). The gastritis is not caused by local irritation alone, because it has followed the injection of "Butazolidin" (Kuzell *et alii*, 1952; Davies *et alii*, 1952; Cudkowics and Jacobs, 1953).

In two cases stomatitis accompanied gastritis, and in seven others the patients had stomatitis only. In none of these was the blood picture altered, and all recovered quickly.

In 13% of cases the patients have had œdema—usually of the lower limbs, but occasionally of the hands or the face. A larger number of patients put on two or three pounds without œdema. It is especially common in the old; acute heart failure may be precipitated (Steinbrocker *et alii*, 1952; Stephens *et alii*, 1952; Bourne, 1953).

In 7% of cases a transient maculo-papular rash occurred. Three patients who also had gastritis were quite ill for a few days; the others did not feel very sick.

In 15% of cases the patients developed transient minor central nervous symptoms (headache, depression, irritability, lassitude). One became disorjented after taking five tablets, and next day had a succession of epileptic fits. Davies *et alii* (1952) saw a patient who died in convulsions after having 1·0 gramme injected daily for nine days.

One patient developed severe hæmolytic anæmia (6·0 grammes of hæmoglobin per 100 millilitres). I have not encountered neutropenia or any other cases of anæmia in spite of regular blood examinations. Severe cases of neutropenia have been reported (Loxton *et alii*, 1952; Crowther and Elgood, 1952; Jarvis, 1952; Tait, 1952; Hinz *et alii*, 1953), with two deaths (Medico-Legal, 1952; Annotation, 1953). Routine follow-up investigations of more than 1100 cases show that blood disorders are exceedingly uncommon (Currie, 1953—343 cases; Kuzell *et alii*, 1952—140; Shulman, 1952—237; Bach, 1952—50; Davies *et alii*, 1952—70; Stephens *et alii*, 1952—188; Steinbrocker *et alii*, 1952—192). Belart (1952), after four years' experience with "Irgapyrin" and "Butazolidin", reports but one case of fatal neutropenia, which he attributes to the amidopyrine moiety of "Irgapyrin".

The Significance of "Butazolidin".

There is no electrolyte shift or change in ketosteroid excretion even when widespread rheumatic inflammation has been suppressed by "Butazolidin" (Currie, 1952; Kuzell *et alii*, 1952). It probably does not act in the same way as cortisone. Its action on rheumatoid inflammation is less powerful and less constant than that of cortisone. But it is more valuable than cortisone in its effect on the pains of osteoarthritis and fibrositis.

The question has been asked: Is "Butazolidin" merely analgesic, or has it a specific effect on rheumatic inflammation (Editorial, 1952)? The following evidence suggests that it is specifically antirheumatic.

1. Pains from other pathological conditions (cellulitis, acute gastritis, headache, traumatic inflammation, carcinomatosis of the spine, sciatica from carcinoma of the pancreas) have not been relieved.

2. In 20 cases acute swelling of a single joint has subsided dramatically at the same time that the pain has been relieved; the joints were not rested.

3. "Butazolidin" is quite unlike aspirin and the other mild analgesics, which have slight and inconstant effects within an hour or two. Its effect takes twelve hours to develop.

"Butazolidin" is still *sub judice*. After treating dozens of patients for three to four months with no ill effects, we get the impression that the reports stressing the dangers are exaggerated. When cases of hæmolytic anæmia and convulsions appear we must be prepared to change that impression.

We await further information from larger series of cases.

Summary.

1. In oral doses of 0·4 or 0·6 gramme per day, "Butazolidin" is a powerful antirheumatic drug.

2. Pain was appreciably relieved in 63 out of 70 courses of treatment given to 55 patients with various rheumatic disorders.

3. Though relief was usually greater in cases of osteoarthritis and fibrositis than in rheumatoid arthritis, several acutely painful and swollen joints settled down rapidly.

4. The pain usually recurred soon after withdrawal of the drug.

5. Though 23 patients complained of nausea, localized œdema or a general eruption, treatment had to be terminated in only two cases.

6. Further experience of 260 cases indicates that "Butazolidin" is not without its dangers; treatment should be interrupted as soon as side-effects appear.

Acknowledgement.

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VALUE OF SERIAL BIOPSIES FOLLOWING IRRADIATION OF CARCINOMA OF THE CERVIX.

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DESPITE careful work at cancer clinics all over the world, including our own in Australia, we are still left with many different schools using varied standard principles of treatment, and all arrive at about the same five and ten year cure figures. The three principal methods are surgical treatment alone, irradiation alone and combined therapy, and a careful study of the available figures with each of these methods leaves the impression that no matter which is adopted in expert hands, the cure rate is of very much the same order. But the histopathologist is showing us that we are dealing with almost two different forms of disease when we treat anaplastic carcinoma and well differentiated carcinoma, and if in either case irradiation can be proved to be inadequate, then a clear case is made out for early radical surgery. This is now possible by assessing the radio-curability of carcinoma of the cervix following irradiation by the method of serial biopsies.

It is also known that a radio-sensitive growth is not necessarily radio-curable and actually may be the reverse, and that such a growth which is resistant to radium can be shown to be so by serial biopsy, and in these cases only radical surgery should be undertaken. In all other cases radium irradiation combined with deep X-ray therapy has proved as effective as any method of cure, especially in early cases, without the operative risk associated with a properly performed Wertheim operation.

System of Serial Biopsies.

During the last eighteen months some of us commenced to follow the work pioneered by Glucksmann and Spear in assessing the radio-curability of cancer of the cervix by serial biopsies before and after irradiation. We have done so because this system claims a 90% degree of accuracy in the prognosis of irradiated tumours, which has been supported by clinical observation, and we felt that an

unfavourable response following irradiaion left no doubt of the necessity for early radical surgery.

The outline of the system is to take a first biopsy and then irradiate the tumour with either a modified Stockholm technique or the Paris technique. The former is better for differentiated tumours and the latter for anaplastic tumours. The advantage of divided doses is that irradiation can be suspended at approximately 5000 milligramme-hours if radical hysterectomy is to be performed. This will avoid necrosis, which may occur in up to 20% of cases after full dosage and radical surgery.

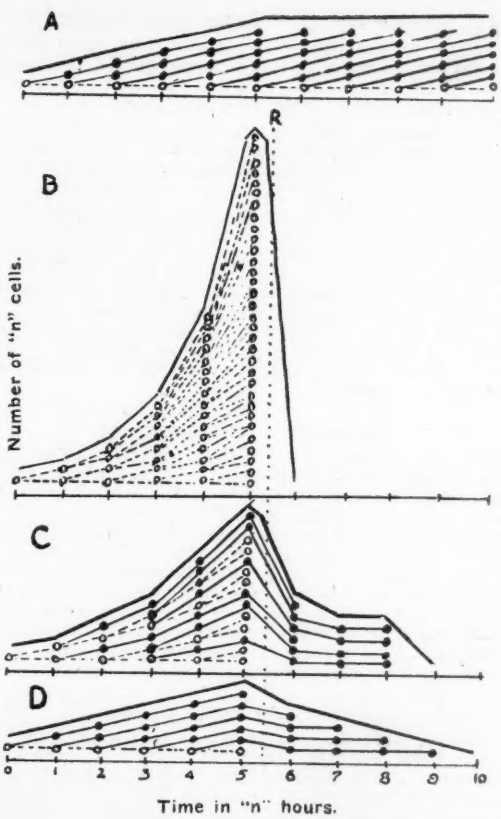

FIGURE I.

Diagram illustrating the varying response to a similar dose of irradiation: B (a highly anaplastic tumour), C (a 50% differentiated tumour), D (normal tissue). A shows normal tissue in growth equilibrium. The circle represents the resting (potential dividing) cell; the solid point represents the differentiating (keratinizing) cell. R indicates exposure to radiation. From Glucksmann (*British Journal of Radiology*, June, 1941).

Serial biopsies are taken one, two and four weeks after the application of the first dose of radium. If the reaction is favourable, deep X-ray therapy is commenced. If it is unfavourable and the patient's condition is operable, then Wertheim hysterectomy is undertaken within six weeks.

Radio-Sensitivity and Radio-Curability.

The stimulating work of Glucksmann first recorded in detail the cellular changes that occurred in tumours following irradiation, and plotted graphs showing the tendencies of the main categories, as follows: (*a*) mitotic or dividing, (*b*) resting, (*c*) differentiating, (*d*) degenerating, following irradiation (Glucksmann, 1941). They showed that a fall in the number of resting cells and a disappearance of mitotic cells were necessary for a favourable reaction to radium, and there was an associated rise in differentiating and degenerating cells. The continued presence of mitosis seven days after irradiation meant that the tumour was still active.

Glucksmann (1948) first demonstrated that the radio-sensitivity of a tumour is no measure of its radio-curability, which is an estimate of the non-appearance of activity in the tumour or regional glands for a period of five years. He has shown that anaplastic tumours, which are the most radio-sensitive cervical tumours, are also the most likely to recur.

The diagram in Figure I illustrates the varying response of a highly anaplastic tumour (I (B)), a 50% differentiated tumour (I (C)), and normal tissue (I (D)) to a similar dose of irradiation (Glucksmann, 1948).

If we assume a life span of n hours for a resting—that is, a potentially dividing—cell, a life span of $5n$ for a differentiating—that is, keratinizing—cell, and an intermitotic period of duration n after each daughter cell divides again while the other differentiates, we arrive at a normal tissue equilibrium after an interval of $5n$, shown in Figure I (A). So the volume of the normal tissue remains constant as the rate of death of each keratinized cell is replaced by cell division.

It is known that the degeneration of a resting cell takes place in one to seven hours and mitosis in thirty to sixty minutes, that the duration of the intermitotic period is 0·5 to 5·0 days, and the keratinization takes three to five weeks.

In Figure I (B) we see the case of a tumour in which all the cells divide up to time $5n$, and R represents the effect of irradiation on the tumour cells and its rapid regression in size.

Figure I (C) shows a tumour in which 50% of the cells differentiate at intervals of $2n$. Again the slower increase in volume of the tumour is shown up to point R, where irradiation has a much slower effect in producing regression of the tumour.

Figure I (D) shows the irradiation effect on normal tissue.

The regression effects are as follows. Tumour regression is complete at $6n$ for the anaplastic growth (Figure I (B)), at $9n$ for the 50% differentiated tumour (Figure I (C)), and at $10n$ for normal tissue.

So it is shown that the same irradiation effect may be reflected in a different rate of macroscopic tumour regression. Rapid tumour shrinkage means destruction of short-lived anaplastic cells, and slow regression the persistence of differentiated cells but without the power of reproduction.

Table I shows some results of irradiation on anaplastic and differentiated squamous carcinoma of the cervix over five years. The radio-curability of such cervical tumours is up to 76% in Stage I against 65% for similar anaplastic tumours. Glucksmann (1948) also shows that the radio-curability, as well as varying with the degree of differentiation of a tumour, varies inversely with the growth coefficient and the tendency to regional and distant metastases.

Table I, from the records of Glucksmann and Spears, shows interesting results in the selection of patients with cervical carcinoma for treatment by irradiation. This table shows a 51% five-year cure rate for all stages of differentiating cervical tumours against 32% for anaplastic tumours. This result is as high as any other five-year figures published after selection of patients and treatment by any other method.

Assessment of Biopsies After Irradiation.

Glucksmann points out that the capacity for increased differentiation of a tumour cell under irradiation distinguishes most of the radio-curable tumours. Differentiation refers to ability of a cell to undergo keratinization or gross enlargement. This capacity renders such a cell incapable of further mitotic activity. This means that some resting cells are destroyed and others differentiate in

a radio-curable tumour, and all mitosis ceases and mitotic cells are destroyed—all within a few days after irradiation.

The assessment of biopsies can be carried out only by comparing biopsies prior to irradiation with serial biopsies following irradiation, and all biopsies must be taken from the growing edge of the tumour mass, and preferably by one experienced operator.

The absence of mitosis in these serial biopsies and the disappearance later of resting cells are evidence of a favourable response, while the persistence of mitoses or of resting cells demonstrates a resistance to irradiation that requires surgical removal of the tumour if it is operable.

TABLE I.

Clinical Stage.	Anaplastic Type.		Differentiating Type.	
	Number of Cases.	Five-Year Cures.	Number of Cases.	Five-Year Survivors.
I	58	64%	38	76%
II	231	45%	161	65%
III	391	27%	186	42%
IV	134	3%	39	7%
	818	32%	424	51%

The presence of normal and abnormal mitoses seven days after a single radium insertion is one (and by itself very often a sufficient) sign of an unfavourable response. Absence of mitosis at the same time is not by itself a sufficiently reliable indication of a favourable response.

In a number of cases cells capable of division (resting or viable cells) are present four or five weeks after a full course of treatment. We must conclude that the tumour, though inhibited in its growth rate, has not been eliminated. These cells are capable of recovery and can lead to a recrudescence of growth. The ultimate prognosis is thus unfavourable, although treatment may achieve a palliative result.

Incidence of Favourable and Unfavourable Reactions to Radium.

There is considerable evidence now that the vast majority of growths showing a favourable reaction to radium are in Stages I and II when operated on—that is, about 95%—and the remainder are distributed through the more advanced stages (Way, 1951).

These favourable tumours also show a differentiating cellular structure in about 80% of cases in the pre-irradiation biopsy.

By contradistinction, when the irradiation reaction is unfavourable, as occurs in 64% of cases, we find 76% are anaplastic tumours (Way, 1951). Only 25% of the unfavourable tumours are operable, as they mainly occur in Stages III and IV, and so the total operability rate for carcinoma of the cervix under this system would be about 16%, which closely approximates the operability rate at the Chelsea Hospital (Read, 1948).

In a group treated by irradiation only, Glucksmann states that in favourable Stages I and II cases 60% of patients were alive at the end of five years, and that in addition to these 26% died of proven intercurrent disease.

In the unfavourable group of Stages I and II treated by irradiation only 11% were alive at the end of five years.

Comparison of Five-Year Cure Figures.

Now let us examine some figures from Australia and overseas which can give some comparison of the relative values in all stages of the various methods of treatment of carcinoma of the cervix after five years.

These figures in Table II show us that the best results over five years from all cases come from Paris, while the Sydney Hospital and Royal Prince Alfred Hospital figures are much the same, with a five-year cure rate of 32·1%.

Similarly, if taken stage by stage, the figures show a close similarity in Stages I and II, but the radium and surgery combined technique shows the best figures in Stage III. But against this, radium alone shows at the same hospital very much the worst figures, and this may be explained by the obvious explanation that radium has been used for the growths least suited for surgery in each grade, and these usually are the worst and most progressive growths, with a large proportion of unfavourable reactions to irradiation.

Comparison of Ten-Year Cures.

There is a definite swing in the later stages in favour of those patients selected for surgical treatment. It will be seen that there is no appreciable difference in the Stage I results, no matter which method is employed, and radium therapy alone has a ten-year cure rate of 50% in Stage I. (Table III.) But there is a great swing in favour of surgical treatment in those cases in which the growth is commencing to progress—especially, in the Stage III growths—and these are the cases in which there is usually an unfavourable reaction to radium, as has already been demonstrated by Glucksmann and Spear, as the groups containing most radio-resistant tumours.

Value of Deep X-Ray Therapy.

There seems to be some evidence that X-ray therapy is of undoubted value in Stages III and IV. I have shown figures for a 20% five-year cure rate of such tumours by Baclesse, of Paris (1950), from the Marie Curie Institute, by the use of deep X rays alone. The State University of Iowa reports a 5% cure rate with deep X-ray therapy alone in later stages of the disease.

TABLE II.

Comparative Figures: Five-Year Cures (Absolute).

Hospital or Worker.	Stage I.	Stage II.	Stage III.	Stage IV.	Total.
Royal Prince Alfred Hospital:					
Radium therapy alone	66·7%	26·8%	15·8%	4·5%	32·1%
Radium therapy *plus* surgery	67·6%	61·1%	44·8%	—	
Surgical operability rate	90·25%	76·0%	40·0%	—	—
Sydney Hospital:					
Radium *plus* deep X-ray therapy	62·5%	43·7%	21·8%	2·8%	32·1%
Marie Curie Institute (Paris):					
Radium	80·0%	61·5%	31·4%	6·0%	34·9%
Deep X-ray therapy alone	—	—	—	—	20·0%[1]
Women's Hospital, New York:					
Radium *plus* deep X-ray therapy	63·6%	53·9%	22·8%	—	27·6%
Victor Bonney, London:					
Surgery alone	—	—	—	—	25·0% (rel. 40%)

[1] Relative figures; deep X-ray therapy alone (only Stages III and IV).

TABLE III.

Comparative Figures: Ten-Year Cures (Absolute).

Hospital or Worker.	Stage I.	Stage II.	Stage III.	Stage IV.	Total.
Royal Prince Alfred Hospital:					
Radium therapy *plus* surgery	61·8%	52·9%	42·0%	—	26·7%
Radium therapy alone	50·0%	30·7%	7·4%	3·6%	
Sydney Hospital: Radium *plus* deep X-ray therapy	55·0%	33·9%	8·8%	—	21·6%
Marie Curie Institute, Paris: Radium *plus* deep X-ray therapy	63·6%	41·9%	22·4%	1·8%	22·9%
Women's Hospital, New York: Radium *plus* deep X-ray therapy	60·0%	44·7%	14·0%	—	18·9%
Victor Bonney, London: Surgical treatment alone	—	—	—	—	Absolute 20% Relative 30% Operability rate 63%

Recurrences.

Baclesse, of Paris (1950), has followed up 56 uncured patients with Stage I growths until death. These patients were all unsuccessfully treated with irradiation. At post-mortem examination the causes of failure were as follows: local recurrence at the cervix, 12 cases; spread to the parametrium, 14 cases; lymph node involvement on the pelvic wall, 10 cases; distant metastases—iliac, abdominal, supraclavicular lymph nodes and lungs, liver and bones—20 cases. This could lead us to believe that in 20% of

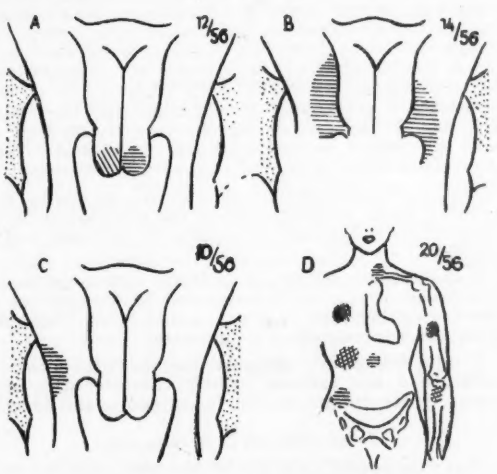

FIGURE II.

Showing site of recurrence in 56 uncured (Stage I) carcinomata of the cervix. A = cervix, B = parametrium, C = lateral pelvic lymph nodes, D = distant metastases. (From the Curie Foundation, Paris; presented at the thirtieth annual meeting of the American Radium Society, Chicago, June 20-30, 1948.)

cases of early carcinoma of the cervix the patient is beyond the reach of any cure by virtue of early and distant metastases (Baclesse, 1950).

Way has shown us that node involvement is much more common with growths resistant to radium, the actual rate of involvement of lymph nodes being 49% in cases of unfavourable radium reaction and 29% in favourable cases.

Glucksmann states that the pattern of distribution of secondary deposits appears to be far more regular than expected and is linked with certain features of tumour histology. He also states that he has been able to predict with a degree of accuracy the presence of involved nodes from the appearance of lymphatic emboli in the pre-treatment biopsy.

Examination of Selected Cases.

Table IV shows the similarity of and improvement in figures that result from selection of cases. Here cases of surgery alone, radium and surgery combined, and irradiation are set out, the greatly improved results resulting from selection being shown. It is also to be noted that the better figures are in inverse proportion to the operability rates.

TABLE IV.

Selected Cases: Relative Figures, Five-Year Cases.

Observation.	Radium *plus* Surgery: Royal Prince Alfred Hospital.	Radium *plus* Deep X-Ray Therapy: Lacassagne, Paris.	Surgery Alone: Bonney, London.
Total number of patients examined with a view to treatment	499	181	793
Operability rate	46%	56%	63%
Total number of patients treated (all growths verified microscopically)	232	101	?
Number treated by other methods or not treated at all	267	81	293
Number alive without recurrence at the end of five years	123	52	291
Relative cure rate	52·6%	51·5%	40%

Conclusion.

There is little to choose in the figures quoted above between the results of surgery or irradiation or combined therapy. In selected cases (Stages I and II) the results, whether by surgery or irradiation, can be expected to give similar high cure rates, over both five and ten years.

Recently Meigs has been the first to surpass these figures in carefully selected Stage I and early Stage II growths, but there is an associated ureteric fistula rate of 13·3%.

It is logical to assume that, if we can forecast those cases in groups I and II that are not radio-curable, then radical surgery should succeed in salvaging a proportion of the patients. There is no doubt that the patients most suited for surgery also are those most suited for irradiation. But there is statistical evidence above that there is a greatly improved survival rate when radical surgery is employed in Stage III carcinomata, either in the five or ten year group. It is in Stage III growths that Way has had only 5% of favourable irradiation forecasts. So it must be expected that irradiation will not do well in Stage III or IV, as in a great proportion of cases an unfavourable response will be produced by the Glucksmann-Spear system outlined above.

Summary.

1. The assessment of serial biopsies following irradiation of carcinoma of the cervix has been described.

2. A description of radio-sensitivity has been given and its distinction from radio-curability made.

3. Figures have been given showing the difference existing between the radio-curability of anaplastic types of carcinoma of the cervix and differentiating types of carcinoma of the cervix.

4. Comparative figures are given of five-year and ten-year cures by various methods of treatment of carcinoma of the cervix.

5. Sites of metastases and their frequency have been described.

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VIRILISM IN THE ADULT FEMALE: ITS DIAGNOSIS AND TREATMENT.

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THE manifestation of virilism in the female, be it of mild degree or distressingly obvious, is a source of mental anguish to the unfortunate subject and causes grave psychological damage. Alleviation of the effects of virilism, whether by surgery or by endocrine therapy, can do much to encourage these unhappy victims and to restore them to normal psychological balance.

Accompanying the outward signs of virilism—hirsuties, coarse skin, acne, amenorrhœa or irregular scanty menses—is a change in personality towards the masculine. These patients are usually shy and retiring owing to their hirsuties, and their attitude changes towards the opposite sex. They lose the pleasure they should enjoy in association with males of their own age in a normal social background.

Criticism has been offered that one can do no good by subjecting these patients to a hazardous operation, when daily shaving will remove the facial hairs. I agree with T. E. Wilson (1952) that one will not improve the patient's warped psychological outlook by presenting her with a razor—the production of excess androgen still remains.

The operation of unilateral adrenalectomy in skilled hands carries no greater risk than the operation for partial thyroidectomy. Broster, in a series of cases reported in 1947, had performed 100 adrenalectomies without a fatality.

I have always been interested in this problem of intersexuality in the female, and in 1950 it was my privilege to be associated with Mr. L. R. Broster, of Charing Cross Hospital, London, who is the pioneer of adrenal surgery in Britain. He classifies virilism under four headings: (i) prepubertal virilism, (ii) post-pubertal virilism, (iii) Cushing's syndrome, (iv) post-menopausal virilism.

Prepubertal virilism is outside the scope of this paper, so I shall pass to a discussion of post-pubertal virilism.

POST-PUBERTAL VIRILISM.

The history of patients with post-pubertal virilism is that they develop in a normal female pattern until some years after the menarche. Then in the late teens or early twenties, the menstrual cycle lengthens, menses become scanty and irregular and there may be periods of amenorrhœa. At the same time the patient develops hirsuties of the face, chest, abdomen and limbs. The abdominal hair follows the male pattern—the pubic hair is continued in a triangular pattern up to the umbilicus. The growth of hair on the face is considerable below the level of the tragus of the ear and at varying points on the upper lip, chin and neck. The hair on the limbs becomes excessive, and in Australia, where surfing and outdoor sports play a large part in the life of the young, this may be a very disabling manifestation. The girl develops an inferiority complex, because she is too shy to mingle on the beaches with her companions.

In more pronounced virilism, the chest becomes flattened, the shoulders become relatively wider than the pelvic girdle, the voice deepens and muscular development increases, with a concomitant loss of subcutaneous fat. Breast development is poor. Coarsening of the skin becomes evident, acne develops and these patients usually have strong luxuriant hair on the scalp, well developed eyebrows and a masculinization of the features which is easily detected by the experienced eye. There may be an enlargement of the clitoris. Pelvic examination reveals a uterus of underdeveloped or normal size, and the ovaries may be normal on bimanual palpation. Obesity is not a common feature of this type.

These patients, if married, are prone to sterility.

In post-partum virilism, after a pregnancy, especially when the result is a male or twins, the patient gains an excessive amount of weight, has amenorrhœa or oligomenorrhœa, hirsutism, striæ beneath the skin, coarsening of the features, and acne. Broster attributes this condition to hæmatomata occurring in the adrenal cortex during pregnancy.

CUSHING'S SYNDROME.

Cushing's syndrome is characterized by obesity, hirsutism, disturbance of carbohydrate metabolism, sometimes glycosuria, erythrocythæmia, hyperpiesia, lowered basal metabolic rate and depressed sexual function.

Whether this syndrome is due to basophilia of the pituitary gland, to adenomata of the adrenal cortex, or to hypertrophy of the adrenal cortex, is a difficult matter to elucidate.

If the urinary output of androgen (17-ketosteroids) is raised and it can be demonstrated by periadrenal pneumography that the adrenal glands are hyperplastic, unilateral adrenalectomy is indicated.

Cushing's syndrome and post-pubertal virilism sometimes merge, and the patients exhibit characteristics of both types. These require careful investigation and judgement.

POST-MENOPAUSAL VIRILISM.

Post-menopausal virilism is probably due to the continuance of the androgenic secretion of the adrenal cortex, without the counterbalancing effect of œstrogen, as the ovaries become senile and cease to produce œstrin. This condition does not require surgical treatment unless it can be demonstrated that one or both adrenals are grossly hyperplastic or the seat of a cortical tumour.

HISTOPATHOLOGY.

H. W. C. Vines (Broster, Vines, Patterson *et alii*, 1938) had difficulty in demonstrating the constant presence of any specific pathological feature in the adrenal cortex in cases of masculinization, until the adoption of the ponceau-fuchsin staining method. On examination of the adrenals in a number of cases of clinical virilism, it was found that by the use of this stain, a vivid red granular material could be demonstrated in the cytoplasm of the cortical cells, and generally in considerable amount. It was absent from the cells of the medulla and was not present in appreciable amounts or was entirely absent from the cortical cells in normal adrenal tissue removed at operation from patients exhibiting no signs of virilism.

The method of staining is as follows:

Soon after the removal of the gland, a portion is fixed in 10% formol saline for twenty-four hours. It is then embedded in paraffin wax and sections are cut. After removal of the wax, the sections are placed in a bath of 2·5 grammes of potassium bichromate and one gramme of sodium sulphate dissolved in 100 millilitres of distilled water, and left for twelve hours. The sections are then washed and stained in the following manner: (i) place in ponceau-fuchsin stain for five minutes; (ii) wash in distilled water; (iii) differentiate in 1% aqueous phosphomolybdic acid for five minutes; (iv) tip off excess of acid and without washing, flood with aniline blue (saturated solution in 25% acetic acid) for seven to ten minutes; (v) wash in distilled water; (vi) differentiate briefly in 1% acetic acid; (vii) wash, dehydrate and mount in salicylate balsam—the use of tap-water must be avoided.

In a series of 36 cases of clinical virilism, this characteristic staining reaction was observed in 34. It was not obtained in control subjects exhibiting no signs of virilism, and it was present in the cells of five adrenal carcinomata associated with virilism. It was also present in the cortical cells of the fœtal adrenal of both sexes at certain stages of development.

In the cortical cells in cases of clinical virilism associated with cortical hyperfunction, the fuchsinophile material appears as a bright red granular deposit in the cytoplasm of the cells, chiefly in the *zona reticularis*, less in the *zona fasciculata* and least in the *zona glomerulosa*. When the fuchsinophile material is present in small amounts in the adrenal cortex of a patient exhibiting no signs of virilism, it is usually confined to the cells of the *zona reticularis*.

In the fœtal adrenal, when this test was applied to fresh adrenal tissue of both sexes, it was found that this fuchsinophile material was present in the cortico-adrenal cells of both sexes at certain times, but it was usually absent during the second half of fœtal life. In the male fœtus from the age of nine to twenty weeks the fuchsinophile material was present in the cortical cells with no question of zoning. In the female, fuchsinophile material was present only from the eleventh to the fifteenth week, the disappearance then being rapid. On the assumption that the presence of this fuchsinophile material is related to the presence of an androgen, this would indicate that there is a brief but definite "male phase" in the normal development of the female fœtus, which is terminated at about the time when the pituitary gland becomes a solid gland and shows differentiation into acidophile and basophile cells (thirteen to fifteen weeks). The disappearance of the fuchsinophile material from the female fœtal adrenal cortex may be controlled by a hormone from the now differentiated pituitary gland. Failure of this hormone to terminate the "androgenic" phase in the fœtal adrenal may be the explanation of subsequent hyperplasia of the adrenal cortex in the female and the exhibition of masculinism.

Investigation.

The investigation of a patient exhibiting virilism should be carried out as follows: A careful history should be taken as to the onset of irregular menstruation, the development of hirsuties, a history of hirsutism in near relatives, and changes in the personality. The basal metabolic rate should be estimated, and a radiological examination of the skull should be made to see whether there is enlargement of the *sella turcica*. A full blood count should be made and biochemical investigations carried out.

The hormonal activities of the adrenal cortex are the following: (*a*) regulation of salt and water metabolism, electrolytic balance and capillary permeability (function of desoxycorticosterone); (*b*) synthesis of glucose (function of the gluco-corticosteroids); (*c*) production of androgens (17-ketosteroids); (*d*) production of œstrogens.

With regard to (*a*), investigation may reveal a raised serum chloride level, diffuse œdema of the tissues and a diminished urinary output. With regard to (*b*), an abnormal glucose tolerance curve may be found, with or without the exhibition of glycosuria. The output of 17-ketosteroids (*c*) can be estimated by analysing a twenty-four hour specimen of urine. The normal output for adult females is from five to 10 milligrammes in twenty-four hours, as compared with the male level of 15 milligrammes in twenty-four hours, the latter figure being due to the male hormone from the testis. Levels in excess of 10 milligrammes of androgen excreted in twenty-four hours are suggestive of hyperactivity of the adrenal cortex, since the normal ovary is not known to produce androgens. The output of 17-ketosteroids is diminished in Addison's disease, in Simmonds's disease and in starvation.

In the present series of cases, in which there was clinical evidence of virilism, the 17-ketosteroid output varied from 13 milligrammes to 39 milligrammes per twenty-four hours in cases of adrenal hyperplasia, and in one case in which an adrenal cortical tumour was present, the output was 96·5 milligrammes in twenty-four hours. In another, in which multiple microscopic adenomata of the cortex were found, the 17-ketosteroid output was 29·3 milligrammes in twenty-four hours.

Periadrenal Pneumography.

Periadrenal pneumography has been found to be a valuable aid to diagnosis. A clear-cut representation of the adrenal glands surrounded by air obviates the necessity in many cases for the preliminary laparotomy practised by Broster and also the necessity of exposing both adrenals at operation.

The perirenal insufflation of air was first practised by Carelli and Sordelli (1921), but in this method the air was introduced through a needle directed through the lumbar region into the perirenal tissues. The risk of an embolism when the needle was introduced into a vein or when air was instilled into an already punctured vein has to be considered.

Recently I have put into operation a safe and effective method for demonstrating the shape of the adrenal glands by introducing air by the presacral method. I was assisted in the perfection of the technique and the subsequent radiology by a personal interview with Dr. James Blackwood and Dr. J. Colclough, of the Repatriation General Hospital, Concord.

The technique is as follows:

An area of skin between the tip of the coccyx and the posterior margin of the anus is cleansed and anæsthetized with 1% "Novocain" solution. With the patient lying in the right lateral cross-bed position, a lumbar puncture needle at least four inches in length is introduced into the areolar tissue between the anterior surface of sacrum and the rectum and passed up as high as possible. The left forefinger in the rectum is used to guide the needle and to make sure that the needle has not penetrated the wall of the rectum. Five hundred millilitres of air are then slowly introduced by means of a 20 millilitre or 50 millilitre Luer-Lok syringe connected to a two-way tap. The patient is then carefully turned on to the left side, and a further rectal examination is made to make sure the position of the needle has not altered during the move. A further 400 to 500 millilitres of air are then introduced. The full litre of air will be necessary for obese patients, but for very thin subjects 750 to 800 millilitres may be sufficient.

At the end of the test the patient is encouraged to sit up for a few minutes and then to walk round for fifteen to twenty minutes. A subdiaphragmatic sense of discomfort is complained of. This persists for about twenty-four hours, and patients have complained of a constricted feeling in the neck and emphysema of the cervical tissues. An antero-posterior film is taken at thirty minutes and others are taken at intervals up to six hours. Some of the clearest outlines are obtained at half or one hour; in other cases the best results are obtained at four to six hours. When air is demonstrated round the adrenal glands, left and right oblique films are taken—these prove invaluable in assessing the size of the gland from a different angle.

Excretion pyelography can be combined with periadrenal pneumography.

Detection of Masculinizing Tumours of the Ovary.

Broster employs a preliminary laparotomy to inspect the female genitalia, to search for aberrant chromaffin tissue in the abdomen and to palpate the adrenals. A method

which I have not tried, but which could be theoretically employed, is direct visual examination of the genitalia with the aid of pneumoperitoneum and the use of Hermon Taylor's peritoneoscope.

An advantage of periadrenal pneumography is to demonstrate the presence of both adrenals. As in occasional cases only one kidney is present, so cases of absence of one adrenal gland have been reported; removal of a single adrenal gland would result in death.

TREATMENT.

Hormonal Substitution Therapy.

In mild cases of hirsutism associated with irregular menses, oligomenorrhœa or amenorrhœa, a three months' course of hormonal therapy may be tried. Œstrogen and progesterone may be given by injection in a rhythmical manner, imitating the twenty-eight day menstrual cycle. Four injections of 10 milligrammes of "Progynon" are given at bi-weekly intervals, commencing immediately after the cessation of the menstrual period. On the twenty-second day of the cycle, 10 milligrammes of "Proluton" are injected and this injection is followed three days later by a second injection of "Proluton" (10 milligrammes). This treatment is repeated twice.

If the basal metabolic rate is below normal level, thyroid medication is given simultaneously. At the end of three months, if the menstrual cycle has improved, administration of ovarian hormones can be continued orally, the cyclical pattern still being observed.

A successful case of hormonal therapy is that of Mrs. B.T., aged twenty-five years, who consulted me for facial hirsuties of eighteen months' duration, and diminishing and irregular menses and sterility of three years' duration. This patient was treated before the introduction of periadrenal pneumography.

The patient was a well-developed, rather tall young woman, with wide shoulders and subnormal breast development; mild hirsuties was present on the face; the pelvic organs were normal to bimanual examination. The basal metabolic rate was −9%. The excretion pyelogram was normal. The urinary ketosteroid excretion was 13·2 milligrammes in twenty-four hours. X-ray examination of the skull revealed a normal *sella turcica*, and a hysterogram revealed patent Fallopian tubes. Assay of the husband's seminal fluid gave normal results.

The patient was given injections of ovarian hormone for three months, combined with one grain of dry thyroid extract daily. She became pregnant shortly after this treatment and produced a son. Hirsuties became less evident, but is still present. Her happiness in her motherhood has banished any worries about her appearance for the time being, and no further investigation has been undertaken.

Operative Treatment.

The indications for operation may be summed up as follows.

1. The presence of adrenal cortical tumours demonstrated by raised 17-ketosteroid output and periadrenal pneumography.

2. Hypertrophy of the adrenal cortex demonstrated by the same methods. In cases in which both adrenal glands are hypertrophied, the larger should be removed first. This will cause a drop of 50% in the androgen excretion. After an interval of six to nine months, if symptoms persist, and the 17-ketosteroid output is still raised, a hemi-adrenalectomy may be performed on the remaining adrenal, the risk of hypoadrenalism being borne in mind.

3. Tumours of the adrenal medulla. These are not discussed in this paper as they do not cause virilism.

4. Cushing's syndrome in certain cases, in which the 17-ketosteroid excretion is raised, or if it can be demonstrated by pneumography that the adrenals are enlarged.

Operative Technique.

Broster employs a preliminary exploratory laparotomy. The adrenals are palpated and the ovaries inspected and a search is made for aberrant chromaffin tissue. Many of these patients have bilateral cystic ovaries. Masculinizing tumours of the ovary are not always detected macroscopically. In Case III, reported later in this paper, luteinization of the pericystic tissue (Stein's syndrome) was demonstrated only microscopically after resection of cystic portions of both ovaries.

There are four methods of approach to the adrenal glands.

The first is Young's bilateral approach (Young, 1936), with the patient prone and two surgeons working simultaneously to expose both glands by a high kidney approach. Some of my earlier patients were treated by this method, but the excision of the gland is difficult, and since the introduction of periadrenal pneumography I prefer a unilateral approach, through a high renal incision with resection of the twelfth rib if necessary. If it is desirable to palpate the other adrenal, a small incision can be made in the peritoneum and the hand passed through to palpate the opposite gland directly.

The second approach is the abdominal approach, through a transverse incision across the upper part of the abdomen, with palpation of both adrenals and removal of one transperitoneally.

The third approach is by a high renal incision with resection of the twelfth rib if necessary. Pleural puncture occurs sometimes during resection of the rib, but leads to a temporary pneumothorax only.

The fourth approach—the transthoracic approach through the diaphragm with resection of the ninth rib—is useful for large tumours. With improvement in post-operative care of patients who have had thoracic operations, the convalescence is not unduly prolonged.

The blood supply of the gland varies. The adrenal artery usually arises from the aorta, but accessory arteries may come from the renal artery or the phrenic artery or directly through the upper pole of the kidney. The adrenal vein on the right side may enter the inferior *vena cava* after a very short course. It also may enter the renal vein, and accessory veins may pierce the diaphragm. The anæsthetist should be asked to steady the diaphragm when vessels passing in that direction are being ligated. All vessels should be underrun by means of a thread on a McCormick's dissector and doubly ligated. The wound is closed without drainage.

Cortical extract is given in the twenty-four hours preceding operation. The intravenous administration of saline during operation may be necessary, and the anæsthetist should keep an accurate check on the blood pressure at frequent intervals. A fall in blood pressure (systolic 110 or 100 millimetres of mercury or lower) should be treated by administration of cortical extract, and the intravenous injection of ephedrine or "Neo-synephrin". The administration of cortical extract is continued for forty-eight hours, and the blood pressure is checked at frequent intervals. When the patient is conscious, one drachm of Lugol's iodine in two ounces of saline is given rectally to ward off the post-operative crisis, which resembles that of thyroidectomy. The presence of pneumothorax is detected by means of radiography at the bedside, and patients respond to deep breathing by means of Wolff's bottles. If pneumothorax occurs it is usually transient and clears up within a few weeks.

Post-operative Progress.

Within six weeks it is possible to pull out excess hairs easily, and although these may grow again they do so in gradually decreasing amounts and are easily extracted. Coarsening of the skin disappears, and the face loses its masculine appearance and becomes softer, more rounded and feminine. Menstrual rhythm improves, and the obesity, if present, tends to subside. Œdema of the tissues lessens with improvement in the chloride excretion.

One patient, aged thirty-one years, who had been prematurely grey-haired for three years, was operated on in May, 1952, and now has one inch of black hair growing from her scalp.

REPORTS OF CASES.

CASE I.—This was a case of adrenal cortical tumour. Miss R.W., aged thirty-eight years, was admitted to the Rachel Forster Hospital in May, 1948, for removal of *fibromyomata*

uteri and bilateral cystic ovaries. Her chief symptom was pronounced hirsuitism, especially on the face, where a thick beard made daily shaving a necessity.

On examination, the patient was an excessively shy, withdrawn and introspective woman. She had a very thick fair beard, straight hair, wide shoulders, a flattened chest and an enlarged clitoris; the abdominal and pubic hair was increased. An enlarged irregular uterus and cystic masses were palpable on bimanual examination. The 17-ketosteroid output was 64·5 milligrammes in twenty-four hours. At operation, bilateral cystic ovaries and a uterus containing multiple fibromyomata were removed. The adrenals were palpated, and a cyst about the size of a golf ball was palpated medial to the left adrenal.

She was readmitted to hospital in October, 1948. Physical investigation gave the same results, except that the 17-ketosteroid output had risen to 94·6 milligrammes in twenty-four hours. At operation (October, 1948) a bilateral approach was made with the patient in the prone position. The right adrenal was small and appeared normal. The left adrenal contained a cortical cyst about the size of a golf ball on the medial aspect of the gland. This cyst occupied almost the whole of the cortex, which was stretched over the cyst. The cyst contained old blood clot. Left adrenalectomy was performed, while the right wound was closed by the second surgeon. Convalescence was uneventful.

On pathological examination the adrenal gland was found to contain a large cystic cavity, the cytology of which was not demonstrable owing to pressure necrosis. The centre of the cavity contained old blood clot. Examination of the cortical cells revealed excess lipoid in many of the cells of the *zona reticularis* and *zona fasciculata*. (No ponceau-fuchsin stain was used in this case.)

The patient's psychological outlook improved, her hair became curly and her general appearance improved. The 17-ketosteroid output was 6·5 milligrammes in twenty-four hours. An unusual feature of this case was that the growth of beard on the face did not decrease. The patient was asked to allow the beard to grow in order that she might pull the hairs out, but as she had her living to earn, she refused to do this and continued daily shaving.

CASE II.—This was a case of bilateral adrenal hyperplasia with possible Cushing's syndrome. Miss B.M., aged thirty-five years, complained of hirsutism, of irregular and scanty menstrual periods, and of increase in weight over the last three years. She had been investigated previously at the Royal Prince Alfred Hospital. She had obesity, hirsutism, pronounced striæ over the abdomen and thighs, and an enlarged clitoris; the internal genitalia were normal on bimanual examination. The basal metabolic rate was –18%. The glucose tolerance curve was raised, and transient glycosuria was present. The 17-ketosteroid output was 20·5 milligrammes of androsterone in twenty-four hours. An excretion pyelogram revealed distortion of the upper calyx of the right kidney. Laparotomy in May, 1950, revealed on palpation that both adrenals were enlarged. Adrenalectomy was not performed.

The patient was admitted to the Rachel Forster Hospital in February, 1951. As she was known to have enlargement of both adrenals, she was subjected to presacral periadrenal pneumography, and a very clear film of the enlarged adrenals was obtained, the left adrenal being larger than the right (Figure I). In April, 1951, left adrenalectomy was performed through a left renal incision with excision of the twelfth rib. The adrenal gland was greatly hypertropied, measuring two inches by 3·5 inches by one inch.

Pathological examination of the adrenal gland showed that the cortex was deep yelow. There was no tumour formation. In the hæmatoxylin and eosin stained section differentiation into zones was apparent. The *zona glomerulosa* and *zona fasciculata* had large cells full of clear lipoid droplets and large vesicular nuclei. The *zona reticularis* stained more deeply, though some of the cells had clear cytoplasm. In the differential staining to show fuchsinophile granules, the more deeply staining cells of the *zona fasciculata* and *zona reticulata* were seen to contain red granules and appeared in distinct contrast to the clear cells towards the periphery of the gland. These cells containing red granules were presumed to be those referred to by Broster, Vines and Patterson, seen in all adrenal sections when virilism is present. The hirsutism decreased and the patient felt better. Her psychological outlook was not much improved; but she leads a very dull, secluded life, looking after two invalid parents, one of whom is blind.

CASE III.—This was a case of Stein's syndrome, with probable adrenal dystrophy. Miss R.S., aged seventeen years, was admitted to the Rachel Forster Hospital in October, 1950. She had had amenorrhœa and a growth of hair on the face, body and limbs for the last eight months.

The patient was a thin young girl with luxuriant auburn hair and a heavy auburn beard. Her breast development was normal, and bimanual examination of the pelvic viscera revealed rather firm ovaries, the left slightly larger than the right; the uterus was normal in size. The urinary excretion of 17-ketosteroids was 6·5 milligrammes in twenty-four hours. The basal metabolic rate was –17%. The serum chloride content was normal. Laparotomy in December, 1950, revealed bilateral cystic ovaries. There were small follicular cysts enclosed in an extremely thick white tunica, resembling the *tunica albuginea* of the testis. On palpation of the adrenals, the right adrenal was found to be enlarged and about three times the size of the left. Bilateral partial resection of the ovaries was performed, and it was decided to readmit the patient to hospital in two months for right adrenalectomy.

Pathological examination of the ovarian segments showed that the tunica was extremely thick and fibrous; follicular cyst formation was pronounced, but no evidence of masculinizing tumour was seen. (This report was revised in the light of further knowledge.)

The patient was readmitted to hospital in January, 1951, for right adrenalectomy, but this was not performed. She had had two menstrual periods at twenty-eight day intervals since operation, and all the hair on her face had fallen out. It was decided to observe the patient further and postpone adrenalectomy.

She reported to hospital in January, 1952. For the first time she had become very sensitive to the growth of hair on her face, which had reappeared about four months after the operation; she had become shy and developed a severe inferiority complex, and asked me to refer her to a psychiatrist because she was feeling so miserable about her condition. Her menstrual periods had been regular and normal. The excretion of urinary 17-ketosteroids was 13·8 milligrammes in twenty-four hours, an increase on the previous estimation. A reconsideration of the histopathological findings in the ovarian segments resulted in an amended report. In this it was stated that a thickened fibrotic tunica was present with many follicular cysts. The follicular cysts were surrounded by layers of luteinized cells, which possibly indicated that the patient was suffering from Stein's syndrome (Leventhal and Cohen, 1951).

Stein's syndrome is characterized by menstrual irregularities or amenorrhœa, by a history of sterility in married women, by the masculine type of hirsutism and occasionally by retarded breast development and obesity. The pathological pattern of the ovaries is characterized by enlargement of the ovaries, a thick pearly *tunica albuginea*, innumerable follicular cysts beneath the tunica and pronounced hyperplasia of the *theca interna* cells (Figure II).

Leventhal and Cohen state that it is probable that the hyperplastic *theca interna* may produce an excess of steroid which inhibits true menstruation. The condition is unresponsive to thyroid or ovarian medication. Surgical treatment of the ovaries resulted in restoration of a normal menstrual cycle in each case. Hirsutism was present in seven of the ten cases reported, but operation resulted in reduction of hirsutism in four only of these cases. Leventhal and Cohen state that the mechanism of the production of this pathological accumulation of cysts in the ovaries associated with fibrosis is not fully understood, but is generally considered to be due to a pituitary ovarian hormonal dysfunction.

No mention is made of an adrenal dysfunction. In this case it was known that the right adrenal was three times the size of the left (palpation at laparotomy). A periadrenal pneumograph confirmed the enlargement felt at the laparotomy (Figure III).

On April 24 a right andrenalectomy was performed. The gland was larger than normal, and portion of the cortex appeared to be cystic and the cystic space was coated with a brown deposit which may have been altered blood. The weight of the fixed specimen was 12·6 grammes; pathological examination of the adrenal failed to reveal any cyst or macroscopically evident tumour. Microscopic examination of the gland revealed the usual adrenal structure, with evidence of granules staining with Masson's stain in the *zona reticularis* and *zona fasciculata* (Figure IV). One small adenoma was present, in which there were a crowding together of cells and nuclei at one side and an increase in density of the granular stain.

Within a week of operation patient had been able to extract half the facial hairs easily. The post-operative urinary 17-ketosteroid output was 11·3 milligrammes in twenty-four hours.

CASE IV.—This case was one of post-partum adrenal hyperplasia with adenomata of the cortex. Mrs. B.W., aged twenty-two years, had increased considerably in weight from eight stone seven pounds to twelve stone six pounds since the birth of a female child twenty-one months previously. Hairs had been growing on her face and chest, and she had had coarsening of the skin and irregular menses

for the last fifteen months. She had had only two menstrual periods in 1951, in July and November.

On examination, the patient was an obese young woman with thick black hair and eyebrows, coarse skin pitted with acne, subcutaneous œdema of the face, hands, legs and feet, scattered thick hair on the face and chest, a male distribution of hair on the abdomen, and striæ all over the abdomen and thighs. Her blood pressure was 160 millimetres of mercury, systolic, and 110 millimetres, diastolic. The serum chloride content was not estimated. The *sella turcica* was normal. An excretion pyelogram revealed no abnormality. The urinary 17-ketosteroid excretion was 29·4 milligrammes in twenty-four hours. On vaginal examination the uterus was normal, and the ovaries were normal to palpation. Periadrenal pneumography revealed that the left adrenal was much larger than the right; there was no visible tumour on the film (Figure V).

At operation on January 21, 1952, left adrenalectomy was performed. The adrenal was enlarged to a size of nine centimetres by six centimetres by 4·5 centimetres; it was firm in consistency, overlapping the upper pole of the kidney and extending medially down to the hilum of the kidney, receiving an accessory blood supply from the upper pole of the kidney. Near the medial side of the cortex was a hæmorrhagic friable area, which confirmed Broster's theory that hæmorrhages occur in the cortex during pregnancy.

On pathological examination, the cortical cells contained deeply staining granules (Vines-Patterson method with ponceau-fuchsin stain—Patterson, 1950).

Scattered through the cortex were small microscopic areas of paler staining cells, which were encapsulated and discrete. These were judged to be adenomata exercising a masculinizing effect.

The patient made an uninterrupted recovery, and during her stay in hospital she improved noticeably in looks; she lost the œdema of the face and hands, and the contour of the face became softer and more feminine. When she was examined in March, 1952, the improvement in her appearance continued; she had lost only six pounds in weight, but the hairs on her face and chest pulled out very easily. She had not menstruated. In April, 1952, she reported that her menstrual periods were still absent. On examination of the patient, the uterus was enlarged to the size of a four months' gestation.

A post-operative 17-ketosteroid estimation has been carried out on this patient; her urine contained 17·5 milligrammes of androsterone in twenty-four hours six weeks before delivery. Provided she does not sustain further adrenal damage with this second pregnancy, the excess œstrin induced by the pregnancy should improve her condition.[1]

CASE V.—This was a case of post-partum adrenal virilism or virilism and Cushing's syndrome combined. Mrs. E.J., aged forty years, had gained four stone in weight after the birth of her fourth and last child thirteen years earlier. Her menstrual periods had been irregular for thirteen years. In one year she had had only three periods. The duration was five or six days, and the loss was heavy.

On examination of the patient, she was seen to be obese. Her blood pressure was 190 millimetres of mercury, systolic, and 110 millimetres, diastolic. Hirsuties was present on the face, abdomen and limbs. The clitoris was not enlarged. On bimanual examination, the uterus and ovaries were normal to palpation.

Estimation of the urinary 17-ketosteroid excretion resulted in a figure of 5·6 milligrammes of androsterone in twenty-four hours. (the volume of urine was 1·83 litres), X-ray examination of the pituitary fossa revealed no abnormality. The serum chloride content was 620 milligrammes *per centum*. The chloride content of the urine was 17 grammes per litre of urine (normal, six to twelve grammes per litre). The sugar tolerance curve was raised; the figures ranged from 141 milligrammes to 260 milligrammes *per centum* of sugar at one and a half hours, returning to 204 milligrammes *per centum* at the end of two and a half hours. There was a trace of sugar in the urine at two hours. A blood count gave normal results.

These findings were suggestive of Cushing's syndrome—raised blood pressure, raised sugar tolerance curve, transient glycosuria, high serum chloride content and normal urinary excretion of 17-ketosteroids. A periadrenal pneumogram suggested the presence of a grossly enlarged adrenal on the right side (Figure VI). The radiologist reported that the air seemed to surround two pyramid-shaped bodies at the upper pole of the kidney, and that the possibility of a "duplex" adrenal could be considered (Figures VII and VIII).

[1] She was delivered of a male infant on August 28, 1952.

In August, 1952, right adrenalectomy was performed. The adrenal was thinner than normal antero-posteriorly, but wider, measuring six by five by one centimetres. The apex of the gland extended high up into the phrenic-vertebral angle. On the medial side a leaf-shaped process extended medially and posteriorly under the inferior *vena cava*. This was responsible for the double apex seen in the pneumogram (Figure IX).

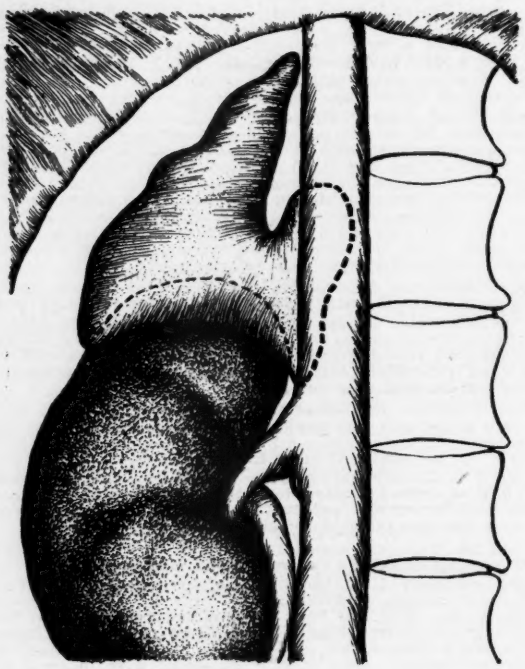

FIGURE IX.

Case V. Drawing of excised right adrenal gland, showing process passing medially and posteriorly behind inferior *vena cava*. This accounts for the "duplex" shadow seen in the pneumogram.

Pathological examination revealed ponceau-fuchsin granules, especially in the cells of the *zona reticularis*, and to a lesser extent in the cells of the *zona fasciculata*. There was no evidence of tumour formation.

CASE VI.—This was a case of hirsutism and virilism due to adrenal cortical tumour. The patient was Miss M.H., aged fifty-one years. Hairs had begun to grow on her upper lip and chin at the age of forty-one years. She had tufts of thick black hair at the corners of the upper lip and also at the mental angle of the chin. The hairs were very long and thick. She had suffered from excessive tiredness for the last few years. The menopause had occurred at forty-eight years. Her sister stated that the patient had become very aggressive and difficult to live with in the last few years. She was very antagonistic to male influence.

On examination of the patient, she was seen to have a considerable growth of hair at the corners of her upper lip and in two tufts on her chin; the hairs were black and about two inches in length. She had no excess hairs on her body. The clitoris was not enlarged, the uterus was small and senile, and no masses were palpable in the abdomen. Her blood pressure was 160 millimetres of mercury (systolic) and 110 millimetres (diastolic). The urinary 17-ketosteroid excretion was 13·8 milligrammes in twenty-four hours. The *sella turcica* was normal. Presacral periadrenal pneumography showed that the left adrenal was enlarged and pushed laterally by a rounded mass the size of walnut. The right adrenal appeared normal (Figure X). A diagnosis of adrenal cortical tumour was made, and operation was decided upon.

On August 30, 1951, left adrenalectomy was carried out through a high renal incision, the twelfth rib being resected. The left adrenal was enlarged and contained a cyst on the medial side of the cortex about the size of a walnut, and appeared to contain old blood clot. The cyst ruptured during handling of the gland (Figure XI).

ILLUSTRATIONS TO THE ARTICLE BY KATHLEEN CUNINGHAM.

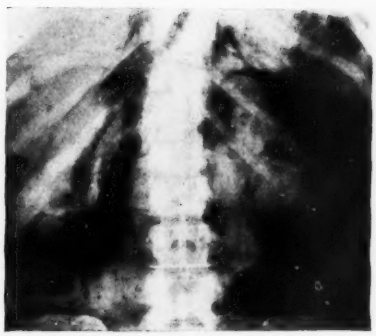

FIGURE I.

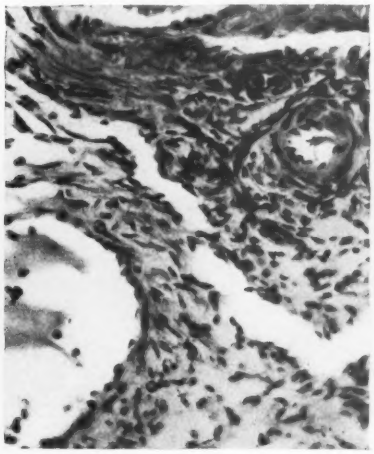

FIGURE II.

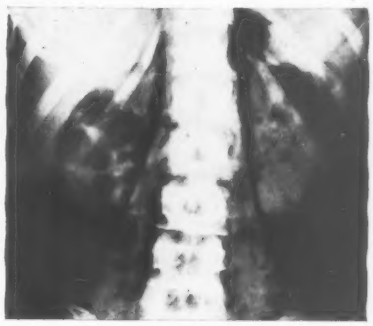

FIGURE III.

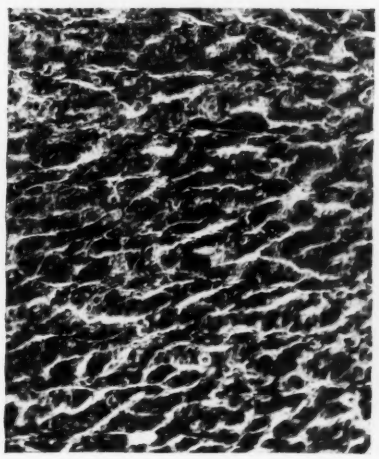

FIGURE IV.

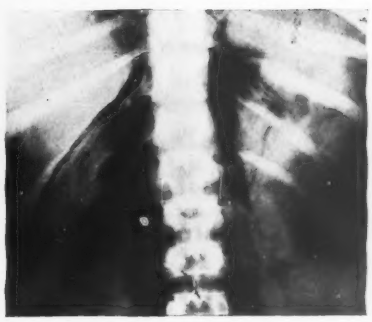

FIGURE V.

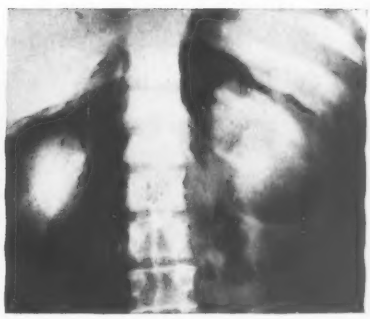

FIGURE VI.

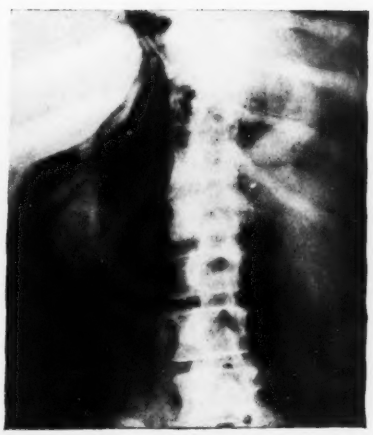

FIGURE VII.

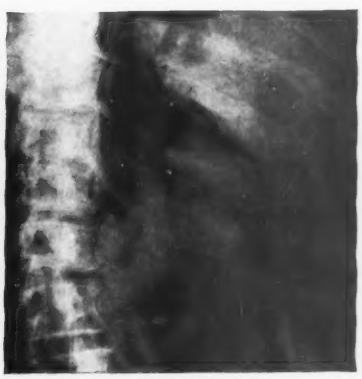

FIGURE VIII.

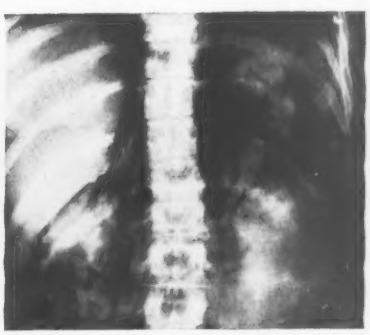

FIGURE X.

ILLUSTRATIONS TO THE ARTICLE BY M. J. J. O'REILLY AND R. E. POWELL.

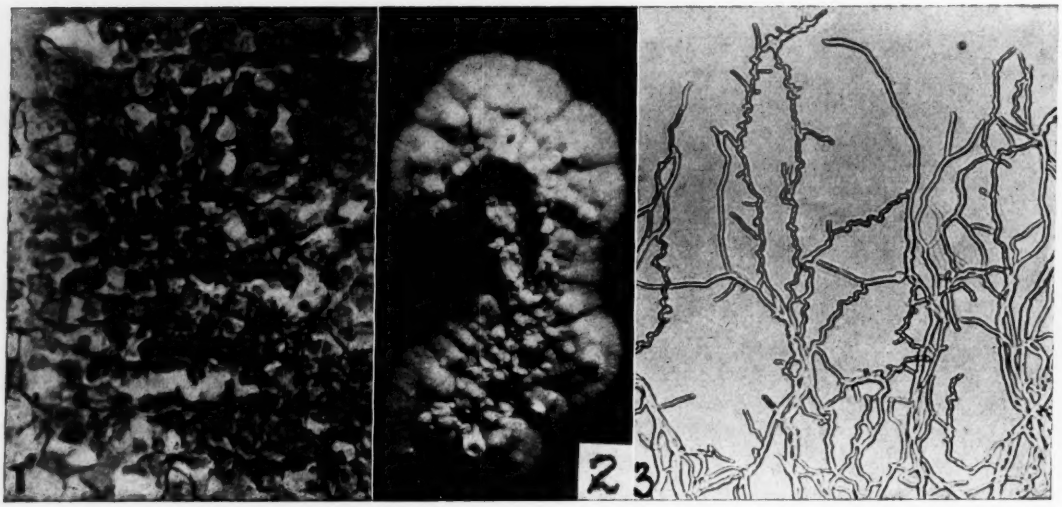

FIGURE I.—Section of lesion of pons, showing *Nocardia asteroides* in the tissue (Gram-Weigert, × 525).

FIGURE II.—Fourteen-day-old macrocolony of *Nocardia asteroides* (× 3).

FIGURE III.—Slide cultures of *Nocardia asteroides*, showing the mycelium beginning to form segments (unstained, × 525).

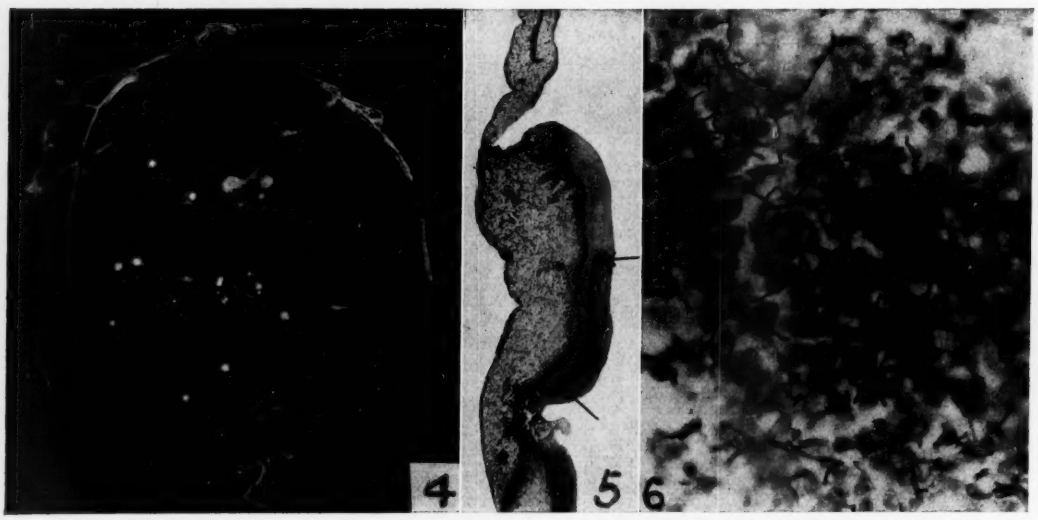

FIGURE IV.—Chorio-allantoic membrane of the chick, showing seventy-two-hour-old infection plaques following inoculum of 10^{-5} dilution (× 1·7).

FIGURE V.—Section of the chorio-allantois, with zone of *Nocardia asteroides* indicated by arrows (Gram-Weigert, × 34).

FIGURE VI.—Section of lung of chick, showing *Nocardia asteroides* growing in tissue (Gram-Weigert, × 525).

Macroscopic examination of the specimen revealed a cystic space on the medial side of the adrenal, the walls of which were stained with brownish deposit. Microscopic examination revealed in the cells of the *zona reticularis* plentiful red granules by the use of ponceau-fuchsin stain; there was less staining in the *zona fasciculata*.

The patient made an uninterrupted recovery. She has been kept under observation for six months and is feeling much better in herself. The hairs on her lip and chin are still growing, but are easily extracted and becoming more sparse. She was examined in April, 1952, when she said that she had not felt so well for years, seemed to be getting on better with her family and workmates, and was very pleased with her improvement in looks and health.

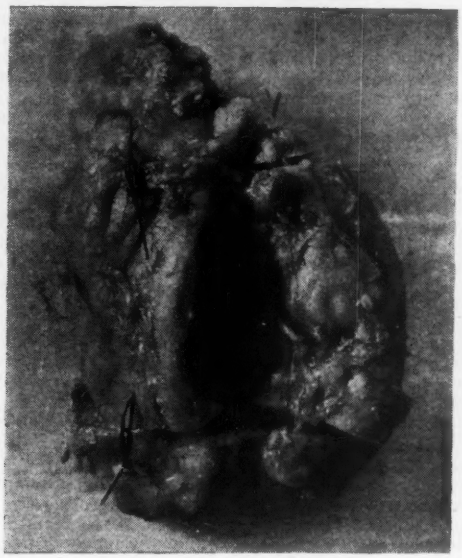

FIGURE XI.

Photograph of excised left adrenal gland, showing cyst cavity on medial side. This was filled with old blood clot and ruptured during handling.

SUMMARY.

An attempt has been made to improve the condition of women suffering from post-pubertal virilism.

Investigation includes estimation of urinary 17-ketosteroid excretion, X-ray examination of the *sella turcica* to exclude pituitary tumour, excretion pyelography, periadrenal pneumography (which in many cases localizes the abnormal adrenal, thus avoiding the necessity of subjecting the patient to two operations), basal metabolic rate estimation, biochemical tests to demonstrate abnormalities of production of desoxycorticosterone and the glucosteroids from the adrenal cortex, a blood count to exclude erythrocythæmia, and laparotomy—inspection of the internal genitalia for masculinizing tumours of the ovary, a search for aberrant chromaffin tumours, and palpation of the adrenal glands.

Treatment has been by hormonal substitution therapy, thyroid and ovarian, or by operation for removal of adrenal certical tumours or of hyperplastic adrenals.

COMMENT.

From a series of some 20 cases, I have endeavoured to present seven, in all of which the diagnosis was not straightforward and in some the issue was confused. A great deal more knowledge is required to elucidate these difficult endocrine problems, and in the light of future knowledge our procedure to relieve these patients may be completely altered.

All these patients are completely satisfied with the results of their operations, are very happy to be able to pull out diminishing quantities of hair, and are unanimous in stating that they feel very much better in general health and that their social adjustment is improved.

ACKNOWLEDGEMENTS.

I wish to record my indebtedness to Dr. Marjorie Dalgarno, radiologist of the Rachel Forster Hospital, for assisting me in evaluating the films in periadrenal pneumography; to Dr. J. C. Drury White for her pathological reports and her interest in the sections; to Dr. James Blackwood and Dr. J. Colclough, of the Repatriation General Hospital, Concord, for their help in reading films and suggesting improvements in technique in periadrenal pneumography; and to the members of the staff of the Rachel Forster Hospital for referring their patients to me for treatment. My thanks are also due to Dr. L. R. Broster, of Charing Cross Hospital, London, for his sustained and helpful interest, both while I was studying at his clinic in 1950 and since my return to Australia.

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Legends to Illustrations.

FIGURE I.—Case II. Photograph of pneumogram showing bilateral enlarged adrenal glands.

FIGURE II.—Case III. Photomicrograph of follicular cysts of the ovary, surrounded by luteinized cells (Stein's syndrome).

FIGURE III.—Case III. Pneumogram showing normal left adrenal gland and enlarged right adrenal, confirmed at operation.

FIGURE IV.—Case III. Photomicrograph showing heavy staining granules in cells of the *zona reticularis* and *zona fasciculata*.

FIGURE V.—Case IV. Pneumogram showing large left adrenal, extending medially to upper pole of kidney.

FIGURE VI.—Case V. Pneumogram showing grossly enlarged right adrenal gland. Antero-posterior view.

FIGURE VII.—Case V. Photograph of pneumogram, right oblique view. This film has not reproduced well, but a pyramidal opaque area can be seen, and medial to this another pyramidal opaque area.

FIGURE VIII.—Case V. Pneumogram. Left oblique view, showing left adrenal slightly enlarged, but small in comparison with the right.

FIGURE X.—Case VI. Pneumogram, showing normal sized right adrenal gland. The left adrenal is displaced laterally by a tumour, which at operation proved to be a hæmorrhagic cyst about the size of a golf ball.

Reports of Cases.

REPORT OF A CASE OF NOCARDIAL INFECTION IN AUSTRALIA.

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Laboratory of Microbiology and Pathology, Department of Health and Home Affairs, Brisbane,

AND

R. E. POWELL,

Queensland Institute of Medical Research, Brisbane.

CLINICAL ACTINOMYCOSIS is usually due to infection with *Actinomyces bovis*, a parasitic, anaerobic, non-acid-fast organism. In about 10% of cases, however (Benbow, Smith and Grimson, 1944), the infecting organism is not strictly parasitic, grows aerobically, and exhibits variable degrees

of acid-fastness. One of the first descriptions of an organism of this type was given by Nocard in 1888, in connexion with a disease of cattle which had hitherto been regarded as tuberculosis. The first human infection was described by Eppinger in 1890 in a case of psuedo-tuberculosis with brain abscess, and he gave the name *Cladothrix asteroides* to the organism which he isolated. This name was later changed by Blanchard in 1896 to *Nocardia asteroides*, and the validity of the latter combination has been confirmed by Waksman and Henrici (1943).

In spite of the comparative ease with which this organism can be cultivated, a review of the literature in 1951 by Connar, Ferguson, Sealy and Conant revealed only 42 acceptable cases, most of which were diagnosed *post mortem*. The only record of human infection in Australia is a case of pulmonary actinomycosis caused by an aerobic acid-fast species of Actinomyces described by Goldsworthy in 1937. Infections of animals are found more frequently. Such diseases as "lumpy jaw" of cattle, caused by *Actinomyces bovis*, mycotic dermatitis of sheep, cattle and horses caused by *Nocardia dermatonomus*, and "mycetoma" in dogs caused by an organism closely resembling *Actinomyces muris*, are reasonably frequent in Queensland, while unidentified species of Nocardia have been found to cause lung diseases and mouth lesions in both wild and domestic animals.

In the great majority of human cases described, the primary infection has been in the lung, with metastatic brain abscesses in about one-third. However, *Nocardia asteroides* has also been isolated from suppurative lesions in other parts of the body. The mortality has been high, and many cases have been diagnosed only at autopsy. Treatment with penicillin and streptomycin has been ineffective, but of the 42 recorded cases, eight patients have apparently recovered after intensive sulphonamide therapy. Such considerations increase the importance of obtaining bacteriological proof by culture in cases suspected clinically to be actinomycosis or tuberculosis, and indeed in any obscure suppurative process.

Clinical Record.

A.S., a male patient, aged forty-four years, was working as a wool-classer at Longreach when, suddenly standing upright, he struck the right side of his head on an iron bar. This injury appeared minor at the time, but later he complained of persistent headache and local tenderness. One week later he noticed that he was seeing double and felt mentally dull. The following day he had some weakness of the left arm and a tendency to stagger. At this stage he was examined by a doctor, who found weakness of the left arm and leg, nystagmus on looking to the left, and thick, slurred speech. No papilloedema was present, and all reflexes were normal. Lumbar puncture produced clear fluid, the pressure not being recorded. An X-ray examination of the skull revealed no fracture. A provisional diagnosis of subdural hæmatoma was made, and he was admitted to the Brisbane General Hospital on the eleventh day after the blow on the head.

Craniotomy was performed on the right side next day, and the left side two days later, with completely negative findings on each occasion. During his stay in hospital he developed severe progressive bulbar palsy and left hemiplegia. His temperature remained within normal limits during his illness, with the exception of a terminal rise to 102·4° F. He died on the twenty-third day after the injury.

A post-mortem examination was made sixty hours after death, the body having been refrigerated during the interval. The relevant findings were limited to the brain and the lungs. The surface of the brain was congested, and a very small quantity of blood was present in the subdural space over each parietal lobe. In the centre of the pons, though extending slightly more to the right, was an irregular abscess two centimetres long and 1·5 centimetres in diameter, which bulged backwards into the fourth ventricle. This abscess contained thick, creamy pus, and part of the right upper wall was hæmorrhagic. The remainder of the brain appeared normal. Bronchopneumonia was present throughout the left lung, except the apex, and also in the base of the right lung.

Examination of sections from the pons revealed the wall of an abscess, in which were numerous Gram-positive, branching mycelial threads. Examination of sections from different regions of the lungs revealed acute bronchopneumonia, with many Gram-positive cocci, but no mycelium could be seen.

Bacteriological Investigation.

Pus from the pontine abscess was collected aseptically, and Gram-positive branching mycelium was seen in smears. The pus was inoculated on to blood agar, Littman's oxgall streptomycin gentian-violet medium, Sabouraud's glucose agar, and glucose acid broth. After twenty-four hours, small pale colonies, one millimetre in diameter, were found on the blood agar. After a week, many small creamy yellow colonies were present on the Sabouraud's slopes. On glucose acid broth, a deep greyish-pink pellicle had been formed, but there was no growth on the Littman's medium.

On Sabouraud's glucose agar, the organism formed slightly stellate, umbonate colonies one to two centimetres in diameter, having raised, dry, opaque centres and flat, moist margins with myceloid edges. These colonies were at first creamy, but quickly became yellow, then deep orange in colour. The production of this orange colour appears to be influenced by light and by heat, being deepest at temperatures below 30° C. and accelerated by the presence of light. At temperatures above 37° C. the colony is a greyish-cream colour, and in the absence of light at lower temperatures it is yellowish-cream. With age, colonies become wrinkled, and partially covered with a chalk-like overgrowth of aerial mycelium. At high temperatures, the colony is more bacterium-like, and the production of the aerial mycelium is inhibited.

Colonies consist of branching hyphæ, 0·3μ to 0·8μ in diameter, in which segmentation behind the growing tip occurs with the formation of oval and coccoid cells. No conidia or other type of fructification were formed, but in older cultures pear-shaped chlamydospores, measuring 1·0μ by 2·0μ, were found.

The organism was identified as *Nocardia asteroides* (Eppinger) Blanchard, 1896, and its cultural characteristics were found to conform to those described by Conant and Rosebury (1948).

The organism is aerobic, Gram-positive and acid-fast. This acid-fast property, however, was found to be restricted to its parasitic phase of growth, all smears from cultures being decolorized by acid, except for the chlamydospores, which retained faint colour when sulphuric acid (1%) in water was used as a decolorizer. It was found to grow readily on plant and animal extract media, but growth was restricted on synthetic media; colony colour was first creamy, later becoming deep orange on all media. Growth in nutrient broth was similar to that in glucose acid broth. On nutrient gelatine, growth was slow, with the formation of a sediment, but the gelatine was not liquefied. Growth on litmus milk was on the surface, with the formation of sediment, and the milk was neither acidified nor coagulated. There was no fermentation or acidification of sugars. The organism was found to have an extremely wide temperature range; the optimum was approximately 42° C., and definite growth was registered at −7° C. and +55° C. The lethal temperature, however, was not determined.

Tests for pathogenicity were carried out on a rabbit, guinea-pigs and chick embryos.

A heavy suspension of the organism from a Sabouraud's slope was made in saline, and 0·5 millilitre of this was injected intravenously into a rabbit, and 1·0 millilitre intraperitoneally into each of three guinea-pigs. The rabbit died in four days, with very numerous, small white nodules (less than one millimetre in diameter) throughout the lungs. A few similar nodules were found in the kidney and spleen, but not elsewhere in the body. Seven days after inoculation, one guinea-pig was very ill, with paralysis

of the front legs, and next day a second guinea-pig became ill, with paralysis of the back legs and apparent blindness. Both animals were killed, and examination revealed numerous miliary nodules in the omentum, spleen, diaphragm and lung bases. The third guinea-pig survived for a month in good condition, and then died suddenly. At autopsy no lesion could be found. The organism was recovered in pure culture from the lesions in the rabbit and the first two guinea-pigs.

A heavy saline suspension of the organism was used, and 0·05 millilitre was inoculated on to the chorio-allantoic membrane of twelve-day-old chick embryos, 0·2 millilitre into the yolk sac of six-day-old embryos, and 0·05 millilitre into the amniotic cavity of fourteen-day-old embryos. The organism was found to cause infection plaques to appear on the chorio-allantoic membrane within twenty-four hours. These plaques were white and opaque, 0·5 to 2·0 millimetres in diameter, and consisted of a proliferation of the membrane cells, with a dense subepidermal invasion by the mycelium of the organism. It also grew readily in the yolk sac, the embryos all dying in two to seven days. There was no detectable embryonic infection. After intraamniotic inoculation, the embryos died in four to six days. The amniotic membrane was found to be pocked with lesions similar to those produced on the chorio-allantois, and the embryo itself was attacked. The embryonic infection was of two types: firstly, there were unbroken lesions on the feet, and secondly there was infection of the lung, which was the only embryonic organ involved. The organism was recovered in pure culture from all infected membranes, yolk and amniotic fluid.

Comment.

No bacteriological investigation of the lungs was made in this case, so it is not known if a primary pulmonary infection existed. However, there was no previous history which would lead one to suspect preexisting lung involvement, nor did the macroscopic or microscopic post-mortem appearances suggest this. The relationship between the head injury and the pontine abscess is also uncertain, but it seems possible that the blow on the head may have produced some bruising in the pons, which provided a suitable nidus for the growth of the fungus, by whatever route it may have reached the blood-stream. Because of the wide temperature tolerance of the fungus, it would most probably have continued to grow saprophytically in the brain tissue during refrigeration.

The growth of the organism over the very wide temperature range is exceptional for most fungi, particularly for those causing disease, but it does lend support to the belief that *Nocardia asteroides* is a common soil inhabitant.

It is interesting to note that the organism was readily adapted to growth in the egg. Its selection of lung tissue in the embryo was unexplained, and was not associated with brain infection, though external lesions on the feet occurred in half the embryos with affected lungs.

Summary.

A fatal case of pontine abscess caused by *Nocardia asteroides* is described, being the second infection in man reported in Australia. It is suggested that infection with this organism may not be uncommon, and that it should be thought of in chronic suppurative conditions, especially in suspected tuberculosis and actinomycosis which cannot be proved by culture.

The cultural characteristics of the organism conformed to those recorded for the species *Nocardia asteroides*. It was found to be pathogenic for the rabbit, the guinea-pig and the chick embryo.

Acknowledgement.

Thanks are due to Dr. A. D. D. Pye, Superintendent of the Brisbane General Hospital, for access to the hospital records.

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Reviews.

A Guide to the History of Science: A First Guide for the Study of the History of Science with Introductory Essays on Science and Tradition. By George Sarton; 1952. Waltham, Mass.: The Chronica Botanica Company. Melbourne: N. H. Seward, Proprietary, Limited. 9½" × 6½", pp. 334. Price: $7.50.

THIS is not a text-book covering in whole or in part the wide area of the history of science; its design is to help the student and teacher of this important branch of history by guiding his reading and letting him know what is being done in various parts of the world. The book opens with an eloquent plea for the proper recognition of the value of the historical approach to the development of scientific ideas, and here the author displays a tolerance not often found in such expositions. Dr. Sarton suggests that an historian of science must have a long and thorough training in the subject. As a rule the author of a history of any branch of science was once a teacher and researcher and then, when his experimental days were over, blossomed out into an historian. Perhaps this is the reason why Oliver Lodge's "Pioneers of Science", which many consider a notable book, is not given a mention. The greater part of the volume is taken up with a very fine bibliography, and there are also lists of societies devoted to the history of science and institutions, museums, libraries and shrines in all parts of the world connected with this study. International congresses are also described and certain prizes which are offered. Dr. Sarton makes it perfectly clear that for the study of the history of science a mastery of the Arabic language is absolutely necessary. When Lockhart and later Draper extolled the culture of the Moors in southern Spain they met with an incredulity not always polite. Dr. Sarton takes in the whole realm of Islamic science and not merely the local burgeoning amongst the Moors. We have but one fault to find, and that is the treatment of J. W. Draper. Here is the entry: "Draper, John William (1811-82), 1874 History of the conflict between religion and science (395 p., New York). Man of science, historian and educator." Now Draper was a professor of physiology and wrote a text-book on this subject with more than one brilliant anticipation of later discoveries. The book mentioned above is good, but is far inferior in scope, scholarship and temper to "The Intellectual Development of Europe" by the same author. This protest uttered, we can only praise highly an invaluable vade-mecum which should be in the hands of every student and teacher of the history of science.

The Old Egyptian Medical Papyri. By Chauncey D. Leake; 1952. Lawrence, Kansas: University of Kansas Press. 8½" × 5½", pp. 108. Price: $2.00.

A SMALL BOOK written by Dr. Chauncey D. Leake, of the University of Texas, will be received by medical historians as a welcome contribution to the better understanding of ancient Egyptian medicine. In the sheltering solitude of the giant redwoods of the Santa Cruz mountains, Dr. Leake and his university colleagues, Dr. Henry F. Lutz, Professor of Semitic Languages, and Dr. Sandford Larkey, Professor of the History of Medicine in the University of California, worked out a preliminary translation and annotation of the Hearst Medical Papyrus, which was completed in 1939.

The opening chapters contain interesting information about the more important ancient Egyptian medical papyri that have thrown light on the beginnings of medical science; and helpful tables show at a glance the approximate date of each papyrus, where it is now located, the name of the translator, when the translation was completed, the condition in which the papyrus was originally found and the nature of its contents. Also, a comprehensive account is given of ancient Egyptian weights and measures, first carefully studied in 1892 by Griffith and Ridgeway, whose work forms the basis of our present knowledge of this complicated

and confusing symbolism. Then follows a dissertation on the vagaries of ancient Egyptian therapeutics before the Hearst papyrus is discussed in detail.

Like some of the better known medical papyri, the Hearst manuscript may have originated many centuries before the present copy was written during the eighteenth dynasty in about 1550 B.C. It was discovered in 1901 by Dr. George A. Reisner while the Hearst archæological expedition was working in Upper Egypt. Reisner made a preliminary study of the papyrus and published a brief account of it in 1905, while Walter Wreszinski, of Königsberg, furnished an accurate and scholarly partial translation into German seven years later. Soon after the somewhat dilapidated scroll arrived in the United States of America, the eighteen sheets or "columns" containing some 255 medical prescriptions were hermetically sealed between glass plates under the expert direction of Professor Edward Gifford, and carefully guarded in the museum of antiquities at the University of California.

In the meantime, Dr. Leake and his two collaborators have prepared a full English translation with their annotations in respect of the diseases mentioned in the Hearst papyrus and the various drugs recommended for treatment.

We can hardly over-estimate the value of this kind of philological research to Egyptologists, medical historians and anthropologists, for the simple reason that it helps to reveal the source of knowledge that was diffused far and wide throughout the ancient world and is still evident in our everyday life. Every medical practitioner with an interest in his profession should peruse the contents of this valuable book.

Disabilities: And How to Live with Them; 1952. London: The Lancet, Limited. 9″ × 6″, pp. 250, with six text figures. Price: 10s. 6d.

FREQUENT it is that praise of a doctor by a patient is heard, but seldom the praise by the patient of the plant that produces the drug that relieved him. Such is one of the experiences of reading this curiously morbid book written by patients of their own diseases and collected and published by *The Lancet*.

It is hard to imagine whom this volume is likely to attract. Medical practitioners are all too familiar with the ravages of incurable diseases and the disabilities they produce, although here and there may be gleaned a way in which one patient overcame his difficulties which can be passed on to another by the medical adviser.

Patients who themselves have incurable diseases might find a little in the two or three articles on the one disease which may help them to solve some of their own problems. In all, this anthology of "diseases best avoided" must have a strictly limited appeal.

The one redeeming feature is the fact that shining through all the terrors of the intolerable burdens borne by ailing mankind, men and women have courage and a will to live through and conquer a multitude of physical and mental difficulties, making this study of the human race an outstanding stimulus to those who may oft-times be inclined to fall by the wayside. Learning to live with oneself with all one's shortcomings and being tolerant of the difficulties of others are admirable principles of which this volume constantly reminds us.

The 1952 Year Book of Obstetrics and Gynecology (July, 1951–June, 1952). Edited by J. P. Greenhill, B.S., M.D., F.A.C.S.; 1952. Chicago: The Year Book Publishers. 8″ × 5¼″, pp. 576, with 98 illustrations. Price: $5.50.

FREE and at times lengthy editorial footnotes characterize this Year Book. However, this is more than justified by the status and experience of the editor, J. P. Greenhill, and by the fact that he uses the footnotes to bring to notice the substance of other related articles not otherwise abstracted. The volume is in two parts, devoted respectively to obstetrics and gynæcology. The subdivision of the obstetrics material is under the headings of pregnancy, labour, the puerperium and the newborn. The section on pregnancy is further subdivided in relation to physiology, abortion, ectopic pregnancy, complications and toxæmia, and that on labour in relation to general aspects, analgesia and anæsthesia, complications, operative obstetrics and uterine hæmorrhage. The section on the newborn deals with practically only obstetrical aspects. The chapters in the section on gynæcology deal with general principles, diagnosis, infertility, operative technique, infections, benign tumours and endometriosis, special ovarian tumours, malignant tumours, menstrual disorders and endocrinology. The book will be of greatest value to the obstetrician, the gynæcologist and the general practitioner, but the general surgeon and to some extent the general physician will find some material of interest.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Recent Advances in Pathology", by various authors, edited by Geoffrey Hadfield, M.D., F.R.C.P.; Sixth Edition; 1953. London: J. and A. Churchill, Limited. 8½″ × 5½″, pp. 384, with 85 illustrations. Price: 30s.

The work of nine contributors, each of whom has dealt with a subject in which he has taken personal interest and has had special experience.

"The Normal Child: Some Problems of the First Three Years and Their Treatment", by Ronald S. Illingworth, M.D. (Leeds), F.R.C.P. (London), D.P.H., D.C.H.; 1953. London: J. and A. Churchill, Limited. 9½″ × 6½″, pp. 352, with 64 illustrations. Price: 30s.

This book deals with problems that arise apart from disease.

"British Pharmacopœia, 1953", published under the direction of the General Medical Council, pursuant to the Medical Council Act, 1862, and the Medical Act, 1950; 1953. London: Published for the General Medical Council by The Pharmaceutical Press. 9″ × 6″, pp. 918. Price: 50s.

This work will become official on September 1, 1953.

"Brain Surgeon: The Autobiography of William Sharpe", with a foreword by Cecil Wakeley, Bt.; 1953. London: Victor Gollancz, Limited. 9″ × 5½″, pp. 244. Price: 16s.

The author, sometime a pupil of the late Harvey Cushing, "blazed the surgical trail" in China.

"Aids to Pathology", by John O. Oliver, M.B., B.S. (London), M.R.C.S. (England), L.R.C.P. (London); Tenth Edition; 1953. London: Bailliière, Tindall and Cox. 7½″ × 4½″, pp. 350, with 16 text figures. Price: 8s. 6d.

One of the well-known "Students' Aids Series"; the first edition of this volume was published in 1907.

"An Atlas of the Commoner Skin Diseases: With 147 Plates Reproduced by Direct Colour Photography from the Living Subject", by Henry C. G. Semon, M.A., D.M. (Oxon.), F.R.C.P. (London), colour photography originally directed by the late Arnold Moritz, B.A., M.B., B.C. (Cantab.); Fourth Edition; 1953. Bristol: John Wright and Sons, Limited. 10″ × 7½″, pp. 380, with 147 plates in colour. Price: 75s.

The purpose of this book is to portray from the living subject, and in natural colour, a collection of the dermatoses most frequently seen in the routine of out-patient practice.

"Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment", edited by Garfield G. Duncan, M.D., with contributions by Walter Bauer, Hugh R. Butt, Abraham Cantarow, Garfield G. Duncan, Frank Alexander Evans, Ferdinand Fetter, Joseph M. Hayman, jnr., Angel Keys, Friedrich Klemperer, Rachmiel Levine, Edward H. Mason, Max Miller, John P. Peters, J. E. Rall, Rulon W. Rawson, Samuel Soskin, Tom D. Spies, Cecil Watson, Abraham White and Priscilla White; Third Edition; 1952. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10″ × 7″, pp. 1198, with 207 illustrations. Price: £7 2s. 6d.

The aim of the book is to bridge the gap between the investigator and the clinician treating patients.

"Varicose Veins", by R. Rowden Foote; Second Edition; 1952. London: Butterworth and Company (Publishers), Limited. Sydney: Butterworth and Company (Australia), Limited. 10″ × 7″, pp. 258, with 186 illustrations, a few in colour. Price: 46s. 6d.

The author has endeavoured to present the "widely divergent views of so many" on the subject. The first edition was published in 1949.

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CHLORAMPHENICOL ("CHLOROMYCETIN").

THE ideal pharmaceutical preparation or drug (as it is commonly called) for use in an illness properly investigated and correctly diagnosed may be described as "the right drug in the right place". In other words it is the drug which will stay the activity of, or kill, the micro-organism causing the illness, or which has been shown by clinical experience to nullify its effects. We are perhaps all liable to forget that therapeutic remedies taken into the mouth or given parenterally have more than the bacteriostatic or bactericidal action for which they are used. It would be absurd to suppose that a therapeutic agent present in the blood in such a high concentration that it would determine the course of an illness would have no general effect on the body or on some of its systems. Sometimes these side effects, as we may call them, are considerable, but in spite of them the drug may still be given. These considerations point inevitably to the folly of the haphazard prescribing of certain drugs, especially when no attempt has been made to arrive at a correct diagnosis. Haphazard prescribing is bad at any time, being the sign of ignorance, or of laziness which is worse; but when such drugs as the antibiotics are concerned it is most reprehensible. Closely allied to haphazard prescribing is a careless oversight of the patient while he is taking a dangerous drug—we all know that untoward side effects may sometimes be detected in an early stage when something can be done to minimize them.

The introduction of this subject has been prompted by the publication of a special survey[1] on chloramphenicol ("Chloromycetin") in relation to blood dyscrasias with observations on other drugs. The authors of the report are: C. N. Lewis, L. E. Putnam, F. D. Hendricks, I. Kerlan and Henry Welch. According to a footnote the report is a compilation and summary of several hundred case records reviewed in July and early August, 1952, by officers of the Food and Drug Administration of the United States, and subsequently reviewed by a committee appointed by the National Research Council. It is pointed out that early in 1950 and subsequently, reports were published about the part played by chloramphenicol in the causation of certain blood dyscrasias. These reports are tabulated and are 19 in number. Many of them were mentioned in these columns on November 22, 1952, in a discussion on chloramphenicol and aplastic anæmia. It is therefore obvious that in certain susceptible persons, chloramphenicol causes blood dyscrasias, including aplastic anæmia, leucopenia, thrombocytopenic purpura and granulocytopenia. The drug may be produced both by clinical synthesis and by fermentation; the result has been that the presence of an impurity in one preparation, but not in the other, has been the subject of speculation. Physical and chemical tests, however, have shown the two preparations to be identical. In 1949, certification of chloramphenicol under the *Federal Food, Drug and Cosmetic Act* was introduced, and since then more than 90% of the drug has been produced by chemical synthesis. "While there appears to be little reason to doubt that the two differ only in their method of manufacture, the possibility of traces of impurities, toxic only to man, in one of the preparations, cannot be excluded without controlled, clinical study." In April, 1952, the United States Food and Drug Administration undertook a nation-wide survey in cities with a population of more than 100,000 to determine the magnitude of the problem. The following information was sought from hospitals and medical practitioners: (*a*) All cases of aplastic anæmia, granulocytopenia, and other blood dyscrasias observed since 1949. (*b*) The name and quantity of each drug or chemical associated with the development of the disorder. (c) The primary disease for which the drug had been prescribed, together with the patient's history, blood data, and other pertinent data. At the time of the writing of the report, 539 cases had been reviewed. The case records used were classified into four groups as follows: A.—Chloramphenicol alone. B.—Chloramphenicol with other drugs. C.—Chloramphenicol not involved. D.—Unclassified owing to insufficient information. Group A included 55 patients suffering from aplastic anæmia with 23 deaths; there were two cases of pancytopenia, four of granulocytopenia, and five of other types of anæmia. The cases in group B numbered 143. There were 95 cases of aplastic anæmia with 73 deaths; there were five cases of pancytopenia, fourteen of granulocytopenia with three deaths, ten cases of thrombocytopenia with five deaths, eighteen cases of other types of anæmia, and one case in which death occurred was grouped under the heading of "Miscellaneous". The length of time over which chloramphenicol was given and the number of courses were investigated. So far as could be determined, there appeared to be no single dosage regimen that was more hazardous than the others used. It is particularly noteworthy that there was an occasional case of reversible granulocytopenia in which chloramphenicol and other drugs were involved, and in which, after recovery of the patient, chloramphenicol was used as a therapeutic "challenge" without untoward effect. The significance of these cases was not made clear. Group C comprised 341 cases. As we are concerned only with chloramphenicol, these need not be quoted in any detail. It is important, however, to note that there were in this group a few

[1] *Antibiotics and Chemotherapy*, December, 1952.

cases of reversible granulocytopenia in which chloramphenicol alone was used later as a therapeutic measure without untoward effect.

When the data had been collected, the National Research Council, at the request of the Commissioner of the United States Food and Drug Administration, called together a committee comprised of several recognized hæmopathologists and internists in order to review the data and to advise the commissioner in regard to any action which might be taken. The opinion of the conference is summed up in the following four statements.

1. Certain cases of serious blood dyscrasias (aplastic anæmia, thrombocytopenic purpura, granulocytopenia, and pancytopenia) have been associated with the administration of chloramphenicol.

2. Although this complication has thus far been uncommon, it is sufficiently important to warrant a warning on the label of packages of the drug and in advertisements of the drug and the recommendation that chloramphenicol not be used indiscriminately or for minor infections.

3. When prolonged or intermittent administration is required, adequate blood studies should be carried out.

4. In view of the paucity of information at the present time, the Conference hopes that further study of serious reaction to chloramphenicol and other drugs will be promoted. The records of the Veterans Administration and military forces could be of great value in providing some of the desired information.

In looking for a conclusion of the matter, we note the declaration in the report that it cannot be stated categorically that the incidence of blood dyscrasias has increased since chloramphenicol became available. It has been shown, however, that chloramphenicol does, in certain susceptible individuals, cause blood dyscrasias. It has been suggested that hypersensitivity may play a role. In opposition to this, it is pointed out that hypersensitivity does not appear to operate, since blood disorders have been reported following one short course of chloramphenicol therapy. The dosage, as already remarked, has little or no bearing on the development of the dyscrasias. There is no doubt that the occurrence of blood dyscrasias with the use of chloramphenicol, or of any other drug, should be reported. The conclusion from the survey may easily be anticipated. It is that the use of chloramphenicol should be based on clear-cut clinical and laboratory evidence pointing to indications for which it is clearly the agent of choice. All the experts consulted in this investigation condemned casual use of the drug, or for that matter, of any potent therapeutic agent for the prevention or treatment of minor infections, since such use may needlessly expose the patient to a serious drug reaction. We may perhaps be pardoned for wondering when practitioners will realize this and act upon it.

Current Comment.

PHENYLBUTAZONE.

In 1949, reports began to appear in continental European literature of the use of phenylbutazone in combination with amidopyrine in the treatment of rheumatic conditions. These reports are listed in an article published by W. C. Kuzell *et alii*[1] in America last year. Phenylbutazone is stated to be one of a group of pyrazole derivatives developed by the chemists of a Swiss drug firm in an attempt to find compounds with pharmacological properties similar to amidopyrine, but without its well-known toxicity. It was found that when phenylbutazone and amidopyrine were used in combination, the solubility of the relatively insoluble amidopyrine was promoted so that it could be given parenterally. It is also stated by R. Domenjoz[1] that a favourable therapeutic effect was achieved with the combination, without the distressing central stimulant action ordinarily met with when amidopyrine is used alone in high dosage. However, it soon became evident that the amidopyrine could be omitted from the preparation without lessening the pharmacological action or therapeutic results. For this reason, recent research has been concentrated on the use of phenylbutazone alone. Domenjoz describes its pharmacological properties, and sums up by stating that its therapeutic effects are analgesic, antipyretic and anti-inflammatory. As a pharmacologist, he considers that the therapeutic effects may, at least in part, be based on the following pharmacological actions, which, he states, have been demonstrated: anti-inflammatory effect, as seen on artificially induced inflammation in laboratory animals; decrease of capillary permeability; antihistaminic effect; antipyretic action; analgesic effect; intensification and prolongation of action of simultaneously administered drugs. The intensity and character of the analgesic action are stated to be very similar to those of the salicylates, the pyrazoles and phenacetin, but not to approach those of morphine.

The paper by Kuzell *et alii* appears to be the first in the American literature. Their study was both clinical and experimental. Clinical trials were carried out on 140 patients suffering from gout and a variety of rheumatic disorders, the phenylbutazone being administered orally and intramuscularly in the proprietary form of "Butazolidin". Parenteral administration was reserved for acute situations. The results quoted may be summed up as follows. Of 48 patients with acute and chronic gout, all obtained some benefit, accompanied by lowering of the serum uric acid level. Of 29 patients with rheumatoid arthritis, all experienced a suppressive effect (21 had a grade 1 or grade 2 therapeutic response according to the American Rheumatism Association's criteria), but symptoms returned promptly four to seven days after discontinuance of medication. Of eight patients with psoriasis and associated arthritis, 11 with ankylosing spondylitis and eight with acute peritendonitis of the shoulder, all responded favourably, as did 10 out of 11 with mixed arthritis. Six women with osteoporosis of the spine in the post-menopausal period gained major symptomatic relief from phenylbutazone combined with sex hormone therapy. The improvement in other groups was less striking or absent. Toxic effects included rash, œdema, nausea, activation of peptic ulcer, vertigo and pain at the site of injection, but the toxicity is described as of a low order, being present in 47 of the 140 cases, and requiring discontinuance of therapy in only 17. From experimental studies with albino rats, Kuzell *et alii* report that phenylbutazone does not alter the pituitary-adrenal axis or produce changes in the blood picture. It causes some inhibition of oxygen consumption, including its utilization in cerebral cortical tissue. As with cortisone and ACTH it aggravates experimental polyarthritis. Shortly after the appearance of the paper by Kuzell *et alii*, J. P. Currie[2] reported his experience with "Butazolidin" in the treatment of 81 patients suffering from rheumatoid arthritis at the Glasgow Royal Infirmary. He administered the drug by intramuscular injection, and, by way of control, in every case substituted for the drug sterile normal saline given for an appropriate period either before or after the period of treatment with the drug; care was taken to ensure that the patients did not know which they were receiving. Currie reports that, of the 81 patients treated with "Butazolidin", 77 stated that their symptoms were relieved—in other words, that their pain was less and that their joints moved more easily. Only 24, however, showed measurable evidence of improvement. Of those 24 patients

[1] *J.A.M.A.*, June 21, 1952.

[1] *Internat. Rec. Med.*, September, 1952.

[2] *Lancet*, July 5, 1952.

with objective improvement, four remained both objectively and subjectively better for periods up to sixteen weeks, eleven relapsed within three weeks, and nine relapsed within twenty weeks. The limited trials suggested to Currie that "Butazolidin" produced a considerable degree of symptomatic relief in acute exacerbations of rheumatoid arthritis, and that, in addition, it did seem to have some anti-rheumatic property. He considers that the drug cannot be just analgesic, as that would hardly explain the observed fall in the erythrocyte sedimentation rate and the measured reduction in the joint swelling. Further, when test doses were given in cases of cephalgia, neuralgia, post-operative pain, pain from trauma *et cetera*, the drug compared poorly with full doses of aspirin. As an anodyne in cases of rheumatoid arthritis, "Butazolidin" appeared to be "quite exceptionally effective".

Subsequent reports have confirmed the symptomatic effectiveness of phenylbutazone, but they have also underlined its toxic properties. These were particularly brought out in a series of letters from various correspondents that appeared in *The Lancet* in the second half of 1952.[1] Untoward effects reported include melæna and hæmatemesis, gastritis, skin rashes, œdema of the feet and ankles and other parts of the body, and agranulocytosis. In most cases, these effects ceased with withdrawal of the drug, but in one case of agranulocytosis, and in one, possibly of hæmorrhagic myelitis, the outcome was in doubt at the time the letter was written. In all these letters there was general acknowledgement of the symptomatic effectiveness of the drug.

Further comparable findings were reported from America in two papers[2] in November, 1952. C. A. L. Stephens, junior, *et alii* treated 188 patients, of whom 147 had either rheumatoid arthritis or rheumatoid spondylitis. Striking subjective improvement was obtained in a high percentage of cases of rheumatoid spondylitis, but the drug was less effective in cases of peripheral rheumatoid arthritis. Objective improvement was less dramatic, but it is described as definite in a small percentage of cases. Stephens and his colleagues stress the high incidence of toxic effects, which occurred in 44% of their patients. They included thrombocytopenia, hæmatemesis, hæmaturia, salt and water retention precipitating heart failure, and the development of duodenal ulcer. In the second paper O. Steinbrocker *et alii* report a "blindfold" therapeutic trial with a number of drugs including phenylbutazone ("Butazolidin"), "Butapyrin" (the phenylbutazone-amidopyrine combination originally marketed in Europe as "Irgapyrin") and placebos. The impressions gained from these preliminary observations are that phenylbutazone and "Butapyrin" are superior analgesics in the painful, chronic, musculo-skeletal conditions studied, and that their effects surpass the suppression of symptoms provided by salicylates, gentisate and amidopyrine. "Antiarthritic" effects of notable degree (that is, an objective response of grade 1 or 2, according to the American Rheumatism Association's criteria) were produced in 23% of cases of rheumatoid arthritis. Steinbrocker and his colleagues are not prepared to state yet whether the effects in cases of ankylosing spondylitis were "antiarthritic" or merely associated effects of analgesia. Again, the proportion of undesirable toxic effects was relatively high. It is stated that none of these were serious, but it was considered wise to cease treatment in 22 cases. A preference is expressed for phenylbutazone over "Butapyrin", because of the hazard associated with administration of amidopyrine.

Another British series is reported by H. Rhys Davies *et alii*,[3] who obtained what is described as remarkable symptomatic relief from the use of "Butazolidin" in a high proportion of cases of rheumatoid arthritis, and an impressive degree of relief in cases of osteoarthritis. They considered the drug to be analgesic and antipyretic rather than curative in its effects. They are satisfied that "Butazolidin" is of value in a wide range of painful skeletal conditions. Relief from pain and increased functional activity have been obtained in cases of ankylosing spondylitis, degenerative joint disease of the spine, and painful Paget's disease of bone. The joint lesions associated with psoriatic arthritis were relieved, but the skin lesions were unchanged. In cases of rheumatic fever the drug was at least as effective as salicylate therapy. In the most recent out-patient cases, oral treatment only has been used. The usual types of toxic effects have been encountered, and Davies and his colleagues state that fluid retention is so common a side effect, though often transient, that they tend to avoid the use of "Butazolidin" in older subjects and in those with diminished cardiac reserve. They do not give it to patients with a definite history of peptic ulceration, and are cautious with those who have severe dyspeptic symptoms.

The question of agranulocytosis has arisen with a striking number of the potent drugs used in modern therapeutics. Phenylbutazone has been no exception. A detailed report of severe agranulocytosis, apparently due to phenylbutazone, has been published by C. Hinz *et alii*,[1] and in their paper they refer to four other cases reported elsewhere in the American literature. In all cases recovery occurred, but the hazard is not to be taken lightly. Attention should also be drawn to a report by V. H. Bowers, which appeared recently in the correspondence columns of the *British Medical Journal*,[2] of a patient who died as the result of acute bilateral hydronephrosis and hydroureter while receiving treatment with "Butazolidin" for gout. *Post mortem* a tight plug of yellowish-brown granular material was found in the lower end of each ureter just above its point of entry into the bladder wall. It consisted mainly of uric acid, with a lesser quantity of urea; no "Butazolidin" was present. Bowers concludes, as did the coroner, that the drug had caused an acute precipitation of uric acid or one of its salts in the urinary tract, either by producing concentrated urine as the result of retention of water in the tissues, or by inducing a massive excretion of uric acid. This is, of course, an isolated case, but it justifies the suggestion made by Bowers that when "Butazolidin" is used in the treatment of gout, a special watch should be kept for the onset of oliguria. If it happens to be due to obstruction of the urinary outflow, as in his case, ureteric catheterization and irrigation may be a life-saving procedure.

The most recently reported British series is that of 50 patients with chronic joint disorder treated with phenylbutazone by L. Cudkowicz and J. H. Jacobs.[3] In 34 cases of rheumatoid arthritis, use of the drug seemed to increase mobility and muscle power and reduce pain to a significant degree; the first two effects appeared to depend on the relief of pain. Cudkowicz and Jacobs consider the analgesic effect, as experienced in cases of rheumatoid arthritis and osteoarthritis, to be phenylbutazone's major quality. Thus, in their view, the drug has a place in the management of chronic joint disease in which the outstanding feature is pain; in their experience, it relieved pain more readily than the usual aspirin-codeine mixture. They observed toxic effects of the usual type in 22 of their 50 patients, and these were often quite severe. They consider that a past history of peptic ulceration or the presence of hypertension, chronic bronchitis and emphysema, or valvular heart disease with a past episode of failure, provides an absolute contraindication to the use of the drug, as cardiac failure may follow salt and water retention. Their conclusions seem to offer a balanced view of the present position with regard to the drug.

The report appearing in this issue of the experience of Michael Kelly, of Melbourne, in the use of "Butazolidin" will be read with interest. Details of all his cases are provided, and should be studied by others who contemplate using this form of therapy. His results are in line with the overseas experience that the drug is particularly effective in relief of symptoms associated with osteoarthritis, fibrositis, rheumatoid arthritis and kindred conditions. Just how far it is justified to call it an "antirheumatic"

[1] *Lancet*, September 20, October 4, October 25, 1952.
[2] *J.A.M.A.*, November 15, 1952.
[3] *Brit. M. J.*, December 27, 1952.

[1] *J.A.M.A.*, January 3, 1953.
[2] *Brit. M. J.*, March 14, 1953.
[3] *Lancet*, January 31, 1953.

drug is still a matter of debate; the term "antirheumatic" probably does not mean quite the same thing to all contributors to the literature on this subject. Kelly's experiences of the side effects of this drug appear to have been happier than those of some overseas workers, but he admits that caution is necessary at present. The practically universal view appears to be that the drug is too effective to be discarded because of its toxic effects; but both medical attendant and patient should be made aware of these, and also of the fact that the action of the drug is suppressive rather than curative.

"MYLERAN": A NEW APPROACH TO CHRONIC MYELOID LEUCHÆMIA.

Two communications from the Royal Cancer Hospital, London,[1] have brought forward a substance, known as "Myleran", of interest and likely value in the treatment of chronic myeloid leuchæmia. A. Haddow and G. M. Timmis describe how the synthesis of "Myleran" was achieved, the work starting from, but eventually moving far afield from, the nitrogen mustards. "Myleran", which has the code name "GT41", is 1:4-dimethanesulphonyloxybutane. D. A. G. Galton reports the results of its use in a two years' therapeutic trial with patients suffering from chronic myeloid leuchæmia. It was given orally according to two schedules: a course of small daily doses over a period of four to sixteen weeks; a concentrated course of large doses given in one to six days. Attempts at maintenance therapy for one to twelve months were made in seven cases. The broad finding in the total series of 19 cases was that "Myleran" depressed myelopoiesis without seriously affecting other hæmatopoietic elements. All the patients responded initially to the treatment, but nine relapsed within six months. Eight patients obtained remissions of between six and twenty-one months; and presumably those were the figures at the time of preparation of this preliminary report and not in all cases the final figures. Galton states that the response manifested by three patients who had received no previous treatment was comparable with the best results of radiotherapy. Five of nine patients for whom radiotherapy was not advised obtained useful, and in four cases "outstandingly successful", remissions. In three cases the response to "Myleran" compared unfavourably with what might have been expected of radiotherapy, but it is suggested that excessive dosage may have been responsible for causing irreversible damage to the bone marrow in one case and may have led to drug resistance in the other two. The only important side effect noted was thrombocytopenia, but Galton thinks it unlikely to be serious if large doses are avoided, and if treatment is withheld when the platelet count is less than 100,000 per cubic millimetre.

Galton points out that for chronic myeloid leuchæmia radiotherapy is the best palliative treatment that has stood the test of time. If a new palliative remedy is to compete with it, the new remedy must be as efficacious and it must be free from undesirable side effects and easy to administer. If it is to take the place of other drugs it must improve on their performance in cases in which radiotherapy is contraindicated. It is particularly important with a new drug to bear in mind that radiotherapy can induce remissions repeatedly; for comparison on this point prolonged experience with a new drug is necessary. The present experience with "Myleran", encouraging though the results are, makes it difficult to give more than a preliminary and tentative assessment of its value, as Galton does not hesitate to state. However, he considers that even if later experience fails to confirm the present impression that "Myleran" is superior to other drugs in respect of the extent of splenic regression, the length of remissions and the rapidity and completeness with which symptoms are relieved, it will still have the advantages of simplicity of administration, absence of side effects and occasional effectiveness after other methods have had to be abandoned. The evidence indicates that any benefit which patients with chronic myeloid leuchæmia derive from "Myleran" probably results solely from the removal of the ill effects of excessive myelopoiesis as a result of the general ability of "Myleran" to depress granulopoiesis. No specific action is apparent. However, the clinical results command attention, and the work should be pursued further.

Incidentally, the short paper by Haddow and Timmis provides a nice example of the sort of chemical and experimental work that precedes the presentation of a new substance for clinical trial. The interested observer, even if he limps rather badly in the chemist's mental footsteps, will be intrigued to see how a train of thought is followed through the almost limitless possibilities of organic chemical combinations.

[1] *Lancet*, January 31, 1953.

INTRAARTERIAL BLOOD TRANSFUSION.

THE value of intraarterial blood transfusion was referred to in these columns on August 30, 1952, in the light of both English and American experience. It is clear that in certain circumstances it has advantages over intravenous transfusion. The defects of the latter procedure are well brought out in a case reported by R. S. Wilson, F. T. Wallace and J. A. Whiting,[1] in which a patient who had suffered from a ruptured ectopic pregnancy was given three and a half litres of blood intravenously in an attempt to combat the effects of massive hæmorrhage and profound shock. The patient died eight hours after the operation from acute pulmonary œdema. It is pointed out that in spite of the fact that adequate amounts of blood were given intravenously to replace fluid loss, sufficient blood did not reach the arterial system to raise the arterial pressure. The left side of the heart was deficient in blood even though there was an abundance in the venous and pulmonary systems. Wilson, Wallace and Whiting state that intraarterial transfusion affords "a means of temporarily taking over the function of the heart by supplying blood to the aorta and then immediately to the myocardium and the brain". They quote the experimental work of Hale, who demonstrated radiologically that opaque medium injected in a retrograde manner into the brachial artery of a dog will reach the coronary, carotid, vertebral and all major cerebral arteries within five seconds. Wilson and his colleagues state that intraarterial transfusion is indicated in cases of sudden cardio-vascular collapse from extensive hæmorrhage. By this means the stage of irreversible shock can be prevented. Severe shock which fails to respond to intravenous transfusion under pressure can be corrected. Patients who have suffered exsanguination in obstetric emergencies and in intraabdominal and intrathoracic operations will respond. Treatment of anæsthetic emergencies, asphyxia and cardiac arrest may be supplemented by intraarterial transfusion. It is recommended that every emergency room and surgical department be equipped for this procedure, which can be lifesaving. The technique is described simply, the usual arteries used being the radial, femoral, *dorsalis pedis* and posterior tibial. Wilson and his colleagues have found the radial artery most satisfactory because of its ready accessibility, its long straight subcutaneous course in the wrist and its ability to accept a 15 to 18 gauge needle or cannula.

Although these advantages in the use of the radial artery will be generally conceded, it is as well to note that ill effects of greater or lesser degree have been associated with its use in this way. M. R. Porter, E. K. Sanders and J. S. Lockwood[2] reported three cases of necrosis of the hand or forearm (one of serious degree) in patients who were given blood centripetally into the

[1] *Am. J. Surg.*, October, 1952.

[2] *Ann. Surg.*, October, 1948.

radial artery. J. Yee, P. R. Westdahl and J. L. Wilson[1] report a case of gangrene of the forearm and hand, necessitating amputation, as the result of radial artery transfusion. They consider that the cause of the gangrene was the perfusion of the extremity with unoxygenated blood for a prolonged period (three hours); vasospasm due to the use of cold blood was a possible contributing factor. In the light of this experience they draw attention to the critical importance of the duration of intraarterial transfusion. Present data are insufficient to indicate the safe limits of volume of blood and duration of transfusion; but, as Yee, Westdahl and Wilson point out, it would seem wise to make the transfusion as brief as possible and certainly to limit it to less than an hour (the period considered safe for the continuous application of a tourniquet to an arm). They add that only whole blood should be used and this should be warmed to body temperature to avoid vasospasm. If significant vasospasm in the extremity is obvious, then procaine cervical sympathetic block is in order. The volume of blood and pressure of the transfusion should be the minimum required to obtain the desired response. In any case, intraarterial transfusion, especially into the radial artery, should not be lightly undertaken.

FATAL ANAPHYLACTIC SHOCK FROM PENICILLIN.

REACTIONS to penicillin are quite common, having been reported in 5% to 10% of all persons receiving this drug. Fortunately the great majority are of minor degree. However, occasionally severe non-fatal anaphylactic reactions have followed parenteral and even topical administration of penicillin. G. A. Higgins and T. P. E. Rothchild[2] describe a case of fatal anaphylactic shock following the administration of 300,000 units of procaine penicillin G, and refer to two instances of fatal anaphylactic shock following the injection of penicillin which have been reported previously. The first of these was a delayed reaction occurring in a debilitated patient following a surgical operation. The second, described by G. L. Waldbott[3] in 1949, occurred in a patient with severe bronchial asthma, who died immediately after the (supposedly intramuscular) injection of 50,000 units of penicillin. Higgins and Rothchild state that their case is the first instance of immediately fatal anaphylactic shock following the giving of penicillin in which a physician was present to observe the reaction and in which an autopsy was performed.

At a meeting of the American Academy of Forensic Sciences held in March, 1952, T. S. Curphey presented a report of two fatal cases of penicillin anaphylaxis with complete autopsy findings. This work, as yet unpublished, is referred to by S. Siegal, R. W. Steinhardt and R. Gerber,[4] who add another fatal case to the list, and describe two instances of non-fatal anaphylactic shock due to penicillin. They believe that other similar cases have occurred, but have not been reported. Even though untold numbers of penicillin injections have been given without serious damage, these increasingly frequent observations of anaphylactic shock should serve as a warning. All but one of the patients concerned suffered from bronchial asthma. The exception is in the case described by Higgins and Rothchild, which therefore is of especial interest. Their patient, a fifty-seven-years-old labourer, entered hospital on April 7, 1952, for excision of a tender lump in the right breast. In October, 1949, he had had an epigastric hernia repaired under local (procaine) anæsthesia. A year later the patient had been admitted to hospital for the treatment of multiple fractures and lacerations following a motor-cycle accident; during his stay in hospital he had received procaine penicillin and had shown no sensitivity to the drug. On the present occasion a small nodule was removed from the right breast with the patient under "Pentothal Sodium" anæsthesia. The operation took place early in the day; the patient was up and walking about by noon and ate the regular noon and evening meals. At 9.25 p.m. an intramuscular injection of 300,000 units of procaine penicillin G was given by the ward nurse, who observed no return of blood on a routine attempt to withdraw the plunger prior to injection. (Four other patients received injections from the same vial.) Approximately one and a half minutes later the patient suddenly became cyanotic and coughed, and a tonic muscular spasm developed. He was examined by the resident surgical officer within thirty seconds of the onset of symptoms. No treatment was of any avail; the man died at 9.35 p.m., ten minutes after the injection of penicillin. Autopsy showed no gross anatomical abnormalities except for increased mucus in the tracheo-bronchial tree. Microscopic examination of the tumour showed gynæcomastia. The authors regret that no blood sample was obtained for antibody studies; however, they are quite convinced that this was a case of true anaphylactic shock. There was no history of allergy, and there had been no reaction to the previous administration of procaine penicillin, so that the high degree of sensitivity evidenced by this patient could not have been anticipated. Consequently, and in spite of the rarity of such a calamity, they counsel that the indiscriminate use of penicillin should be avoided. Certainly there does not seem to have been any indication for its use in this instance.

Siegal, Steinhardt and Gerber discuss the question of prevention in some detail. Firstly, it is obviously wise to avoid the indiscriminate use of penicillin. For many minor respiratory infections chemotherapy should be avoided altogether. Secondly, before penicillin is given, a careful history should be elicited as to its previous administration and the occurrence of any reaction, and also as to any evidence of allergy, particularly bronchial asthma. Siegal and his colleagues believe that a sharp distinction should be drawn between the common delayed reactions on the one hand and the uncommon accelerated or immediate reactions on the other. Immediate reactions, even though mild, are of much more serious import. Finally, it must be remembered that the absence of any previous allergic reaction to the drug by no means precludes the possibility of anaphylactic sensitization. Skin tests may prove to be helpful in the future, but so far experience is too limited to rely on them. Siegal *et alii* insist that the technique of penicillin injections deserves critical appraisal in the effort to avoid anaphylaxis. They suggest that injections, especially the first of a series, should be given into the outer aspect of the upper part of the arm rather than into the buttock or deltoid, so that if necessary a tourniquet, ready at hand, may be applied proximal to the site of injection. Accidental intravenous injection should, of course, be avoided by the routine measure of tugging on the plunger before actual administration. Adrenaline should always be at hand. The foregoing is a bare outline of the discussion given by Siegal and his collaborators. Their description of the various types of reactions to penicillin and of the possible use of skin tests is well worth reading. The precautions outlined are intended particularly for the care of asthmatic and atopic persons; nevertheless, as they point out, all may benefit from greater caution in the use of this valuable antibiotic.

[1] *Ann. Surg.*, December, 1952.
[2] *New England J. Med.*, October 23, 1952.
[3] *J.A.M.A.*, February 19, 1949.
[4] *J. Allergy*, January, 1953.

A SURGICAL HONOUR FOR TWO AUSTRALIANS.

THE Royal College of Surgeons of England has admitted to honorary Fellowship Dr. Robert Scot Skirving, of Sydney, and Dr. Albert Ernest Coates, of Melbourne. Dr. Scot Skirving graduated at the University of Edinburgh in 1881, and Dr. Coates graduated at the University of Melbourne in 1924. This is an unusual honour, and the announcement has been received with much pleasure and satisfaction by the friends and colleagues of both recipients.

Abstracts from Medical Literature.

THERAPEUTICS.

Intractable Peptic Ulcer and Methantheline ("Banthine") Bromide.

D. Liebowitz *et alii* (*J.A.M.A.*, October 18, 1952) report the results of treatment with "Banthine" in a group of 15 patients refractory to the usual medical treatment of peptic ulcer. Their response over a period of months was followed. Of the 15 patients, 10 had gastric ulcer and five duodenal ulcer. "Banthine" was found to relieve symptoms initially in 14 of 15 cases. Of nine ulcer craters seen initially, six disappeared after two to ten weeks. However, during the course of a year, nine patients had recurrences of symptoms, and four developed fresh ulcers while taking the drug.

Hiccups and Myocardial Infarction.

H. S. Swan and L. H. Simpson (*New England J. Med.*, November 6, 1952) discuss hiccups complicating myocardial infarction. They state that the prognosis in this condition is bad, but not many reports have been published. Treatment of post-operative and post-encephalitic hiccups is also unsatisfactory. The authors quote Bailey's statement that drugs are not effective; gastric distension should be relieved, uræmia and pleurisy should be excluded, and then 100% strength carbon dioxide should be given through a mask; as a last resort, the left phrenic nerve should be tied and injected. Quinidine has been reported as of value in some cases. Bilateral phrenic nerve crush is harmless, and has been effective, especially in cases of post-operative and post-encephalitic hiccups. The authors report two cases of myocardial infarction with hiccups in which the patients lived and returned to work. Neither patient experienced orthopnœa or dyspnœa after paralysis of both diaphragmatic nerves. The authors state that hiccups may accompany anterior or posterior infarction. Relief of gastric dilatation is necessary; quinidine therapy should be pushed to the extent of toxicity. If the attack of hiccups persists, fluoroscopic examination should be made to ensure that both sides of the diaphragm are involved, and in that event, bilateral phrenic crush is performed. As accessory phrenic nerves exist, fluoroscopic examination should be repeated after this procedure.

Rheumatic Fever.

J. J. Bunim *et alii* (*J.A.M.A.*, November 29, 1952) discuss cortisone and ACTH in the treatment of rheumatic fever and juvenile rheumatoid arthritis. They report that in cases of rheumatic fever, polyarthritis, chorea, subcutaneous nodules and skin lesions varied in their response to cortisone. Pericarditis subsided, as a rule, in five days, possibly as a result of cortisone therapy. Myocarditis, as indicated by tachycardia, gallop rhythm, electrocardiographic changes or congestive failure, appeared to respond to cortisone or ACTH in acute but not in advanced cases. Organic heart murmurs also disappeared in 11 patients treated; but in others chronic heart disease developed. Cortisone, ACTH and acetylsalicylic acid all failed to prevent organic heart disease. However, hormone therapy was life-saving in several cases. After withdrawal of ACTH or cortisone, fever, tachycardia and other signs often recurred. The authors state that patients with polyarthritis but no carditis need not be given cortisone or ACTH; salicylate is the drug of choice in these cases. Only recent and severe carditis requires hormone treatment. In juvenile rheumatoid arthritis, the hormones give relief, but there may be recurrence, and increased doses may be necessary. The disease may progress in spite of treatment.

Hyperthyroidism.

D. E. Clark *et alii* (*J.A.M.A.*, November 29, 1952) describe five years' experience with radioactive iodine (I^{131}) in the treatment of hyperthyroidism. They state that 384 patients were studied between the ages of eleven and eighty-four years. One month without treatment was necessary for those previously treated. Then 150 millicuries per estimated gramme of thyroid tissue were given to patients under forty years of age, and 250 millicuries to those over forty years. To those with nodular glands, 300 to 350 millicuries were given. The patients were observed at two month intervals, and if a euthyroid status was not obtained, additional radioiodine was given. The response was slower than when iodine (I^{131}) or antithyroid drugs were given concurrently. Those treated had been previously treated in most cases with surgery, Lugol's strong iodine, antithyroid drugs or X-ray therapy. Remissions were obtained in 85% of cases, lasting for six to twelve months. Diffusely enlarged glands decreased in size, nodular goitres sometimes became smaller. Exophthalmos was unchanged in many cases. Complications were rare.

Nor-epinephrine in the Treatment of Shock.

G. S. Kurland and Monte Malach (*New England J. Med.*, September, 1952) report their experiences of nor-epinephrine in the treatment of 30 cases of shock. The results indicate that in practically all cases of shock nor-epinephrine will restore the blood pressure and relieve shock, but whether this improves the prognosis remains unsettled. It is the authors' impression that fewer patients died with this treatment than would have been the case without it. It appears that there were 10 deaths among the 14 cases of myocardial infarction accompanied by shock, and 13 deaths among the 16 cases of shock due to other causes. The authors believe that pulmonary œdema and congestive failure do not detract from the value of this treatment. Data for a comparable control series were not available. The drug was given as an intravenous infusion for periods of ten minutes to six days.

Lobectomy for Pulmonary Tuberculosis.

James H. Forbes (*Ann. Surg.*, November, 1952) presents his results of lobectomy in cases of pulmonary tuberculosis. The indications for lobectomy in his hands are as follows: (i) tuberculoma not suitable for segmental resection; (ii) persistent cavitary disease, including principally one lobe, more certainly if there is branchostenosis of the lobe bronchus; (iii) persistent, chronic, active, non-cavitary tuberculous lesions involving principally one lobe; (iv) certain suspected but unproved chronic tuberculous lesions confined principally to one lobe, exclusive of tuberculoma; (v) failure of thoracoplasty to control the disease. The author discusses the use of streptomycin and para-amino-salicylic acid. He chooses to administer them as pre-operative preparation, and advises their continuance in the post-operative phase as protection against dissemination of the disease. In his hands, the mortality from lobectomy was 0·75%, and early results were good. Complications were few; bronchopleural fistula developed in 3·2% of cases and empyema in 2·7%. Spread of the disease in the six-month post-operative period occurred in only 2% of cases. Some 75% of the patients were in the age group of twenty to forty years, but 2% were aged over fifty-one years. The author concludes that, when indications are followed, lobectomy, with the aid of proper rest and antibiotic therapy, is the safest, surest and quickest method of achieving arrest of the disease.

Fatal Effect of Antibiotic Therapy in Neoplastic Disease.

J. C. Bateman *et alii* (*Arch. Int. Med.*, December, 1952) report fatal complications of intensive antibiotic therapy in patients with neoplastic disease. Large doses of terramycin and penicillin were used. Nine patients with far-advanced cancer and one patient with renal calculi and persistent urinary tract infection were treated with parenterally administered terramycin. In eight cases there was rapidly progressive azotæmia, followed by death. Pronounced hypotension was observed in the majority. Three patients with far-advanced cancer received 12,000,000 units of penicillin intravenously every four hours. Sudden death occurred in two cases, immediately after the third and fourth injections respectively. In the third case, convulsions developed during the third injection and were followed by recovery. A correlation of studies made by others and the facts in these cases suggests that impaired renal function may slow excretion of terramycin and penicillin to such a degree that blood levels ensue which are toxic to the patient.

Nephrectomy for Hypertension.

W. F. Braasch (*J. Urol.*, July, 1952) reviews post-operative results in 100 cases at the Mayo Clinic in which nephrectomy had been performed for hypertension at least two years earlier. Actually, in 60 of the 100 cases, the operation had been performed over five years before. The blood pressure returned to normal or was significantly reduced in 64% of patients traced from two to five years after operation, and in 53% of those traced from five to nine years. The author states that these results should remove any doubt about whether a unilateral renal lesion can cause hypertension, and whether nephrectomy in such cases is beneficial in a healthy proportion. Careful selection of patients for nephrectomy is essential to good results. Any evidence of a lesion in the other kidney, advanced age, unsatisfactory general condition or long duration of the hypertension is a

contraindication to operation. The three pathological conditions most frequently associated with hypertension are atrophic pyelo-nephritis, hydronephrosis with infection, and renal tuberculosis. The blood pressure may drop to normal after nephrectomy, with great symptomatic benefit, and then gradually return to higher levels, with recurrence of symptoms, after an interval of months to years. In such cases it is possible that nephrosclerosis exists in the opposite or supposedly normal kidney, or that dormant essential hypertension is present, the infected kidney having acted as an immediate stimulant.

NEUROLOGY AND PSYCHIATRY.

The Significance of Fatigue.

H. C. SHANKS AND J. E. FINESINGER (*Psychosom. Med.*, July-August, 1952) regard fatigue as a signal to desist from some activity or attitude which has been persisted in too long or too intensely, a warning of danger to the individual's person or to his concept of himself. They state that in a study of 100 patients complaining of fatigue as a primary symptom, it was often found that at the onset of fatigue there was an emotional state of unpleasant nature and considerable intensity in circumstances which prevented expression of the patient's feelings in appropriate action. As the sensation of weariness became prominent, efforts to express the feelings were relinquished.

Schizophrenia in Childhood.

LOUISE F. W. EICKOFF (*J. Ment. Sc.*, April, 1952) states that schizophrenia in childhood has been reported more frequently from America than from Britain. She relates the case history of a girl, aged seven years, the general impression of the patient being one of an inquisitive toddler still at the baby-talk stage and not fully in touch with reality. The child's behaviour was bizarre, and she had the one delusion that she was a boy. The author postulates that schizophrenia in childhood is an arrest in the development of abstract thought and emotional maturity at an infant or toddler level, that this arrest is dependent basically upon a defect in the acquisition of general sensation, and that this in turn is due either to a defect in the neurological systems concerned with touch, pain, temperature, position and vibration senses or to faulty stimulation from outside or both. This defect leads to a delay in the formation of the body image and other images. A scheme of treatment is suggested including remedial measures to aid sensational development.

Long-Term Prognosis in Mental Illness.

W. L. HOLT, JUNIOR, AND W. M. HOLT (*Am. J. Psychiat.*, April, 1952) state that 141 patients were admitted to Westborough State Hospital in 1921 soon after study at the Boston Psychopathic Hospital. Nearly all these patients were investigated thirty years later; only 7% of the group could not be traced. The study included age, diagnosis, time spent in hospital, condition on discharge, community adjustment, age at death and cause of death. In this cross-section sample, 26% of all patients traced had recovered before death or when investigated after thirty years. The *dementia præcox* patients, constituting 42% of the group, accounted for 39% of the surviving patients in the community and 35% of all recovered patients. When the last hospital diagnosis was accepted as valid, 23% of *dementia præcox* patients were recovered at death or when investigated after thirty years. When no significant diagnostic disagreement occurred throughout successive admissions to hospital, only 13% of *dementia præcox* patients recovered.

Relation of Specific Attitudes and Emotions to Bodily Diseases.

W. J. GRACE AND D. T. GRAHAM (*Psychosom. Med.*, July-August, 1952) in a study of 128 patients were able to correlate a particular psychosomatic symptom or disease with the patient's conscious attitude to the precipitating life situation. They state that in many cases the symptom seemed biologically appropriate to the attitude; urticaria, for example, occurred when the patient saw himself "taking a beating". The authors propose that "emotion" be defined as "an attitude with its associated physiological changes".

Partial Removal of Post-Central Gyrus for Pain.

WALPOLE LEWIS AND C. G. PHILLIPS (*J. Neurol., Neurosurg & Psychiat.*, August, 1952) report three cases in which partial resection of the post-central gyrus was undertaken for the relief of pain. The first case was one of pain developed during a sensory aura in traumatic epilepsy, the second one of intractable pain in a phantom foot and the third one of painful thigh stump. In each case electrical stimulation of the appropriate area of the post-central gyrus reproduced the pain complained of by the patient, and relief followed the removal of this area of cortex. The authors question whether removal of these small areas of sensory cortex will permanently relieve pain; but they nevertheless point out the attraction of an operation in which pain is relieved without producing permanent motor or sensory deficit or personality change.

The Pons and Hypothalamus in Poliomyelitis.

H. A. MATZKE, A. B. BAKER, S. CORNWELL AND I. A. BROWN (*Arch. Neurol. & Psychiat.*, July, 1952) report detailed studies of the pons and hypothalamus in over 100 cases of bulbar poliomyelitis. They state that histological studies showed the pons to be involved in nearly every case, with differing severity and distribution. All motor nuclei were equally damaged, the damage exceeding the clinical dysfunction observed. Irritation of the motor trigeminal nerve may cause severe trismus, and involvement of the lower part of the pons with the upper vasomotor centre causes circulatory failure. In the studies of the hypothalamus it was noted that lesions occurred in 85% of cases of bulbar poliomyelitis, the hypothalamus being diffusely damaged, especially the supra-optic nuclei. In the acute illness some patients showed clinical hypothalamic dysfunction in hyperthermia, gastric hæmorrhage and hypertension. Gastric hæmorrhage could prove fatal in an otherwise recovering patient. Months or years after recovery from bulbar poliomyelitis the patient may show evidence of subclinical hypothalamic damage, as revealed by tests of hypothalamic function.

Autonomic Nervous System and Immunity.

S. LOUMAS (*Arch. Neurol & Psychiat*, July, 1952) discusses the role of the autonomic nervous system in the defence reactions of immunity in the body. He considers that in some way these processes are connected with the function of the autonomic system, especially with the hypothalamus, the centre of all metabolic processes, sleep, thermogenesis, water, salt exchange *et cetera*. Through the hypothalamus and pituitary, various physiological conditions (age, puberty, pregnancy *et cetera*) and also some pathological states (obesity, diabetes, thyroid disease) are known to affect the defensive mechanisms of the body. It is also conceded that the hypothalamus is under psychological influence, and that such influence may well affect the general resistance and immunity of the body via the hypothalamic centres. Variable reactions of immunity and degrees of resistance may then be due to individual differences in reaction of the autonomic system, these differences in reaction being largely due to varying psychological factors, as well as the usual physical factors, such as variable toxicity of the agent.

Cerebral Aspergillosis.

S. IYER, P. R. DODGE AND R. D. ADAMS (*J. Neurol., Neurosurg. & Psychiat.*, August, 1952) report two cases of aspergillus infection of the central nervous system and review the literature (10 cases), in which it is recorded that the pathological reaction in the nervous system to fungous infection takes the form of a chronic, suppurative or granulomatous inflammation and that the lesions may be localized either in the meninges or in the brain, the site depending on the route of entry of the fungus. They discuss the pathogenesis and clinical features of their cases, the first being consistent with a chronic localized granuloma of the meninges of the cervical part of the cord and brain stem and the second presenting as chronic encephalitis with progressive dementia, convulsions, spastic paralysis and cerebral calcification. Both cases were fatal; the aspergillus was isolated in autopsy material.

Visual Hallucinations with Occipital Lobe Tumours.

D. PARKINSON, C. W. RUCKER AND W. MCK. CRAIG (*Arch. Neurol. & Psychiat.*, July, 1952) describe a series of 50 cases of occipital lobe tumour, in which 12 patients had hallucinations as a symptom. These were described as lights, rings, circles, flickers *et cetera*, but none were formed hallucinations. There was no relation between tumour type or rapidity of growth and the hallucinations. Raised intracranial pressure occurred in 10 of the 12 cases. The authors state that the series is too small to be of statistical value, but suggest that the findings are compatible with the concept that with lesions strictly limited to the occipital lobe, hallucinations when present are usually unformed and limited to the opposite visual field, and more particularly to the area of the field defect.

Special Article.

THE CAPACITY OF THE MEDICAL PROFESSION IN NEW SOUTH WALES TO ABSORB NEW MEMBERS: A FURTHER REVIEW.

IN THE MEDICAL JOURNAL OF AUSTRALIA, December 18, 1948, a Special Article was published over my name headed "Overcrowding the Medical Profession in New South Wales", in which attention was drawn to the enormous influx of medical students at the University of Sydney and its possible repercussions.

Since then the picture has altered considerably owing to a relatively large increase in the population of this State as a result of immigration, but instead of enrolments in the Faculty of Medicine declining rapidly as was expected, it has kept up at a relatively high level so that it was thought some further analysis of the absorptive capacity of the medical profession in New South Wales for new members should be undertaken. Table I is self-explanatory and shows the position as affecting the Medical School at the University of Sydney since 1944.

TABLE I.

Year.	First Year Enrolments.	Total Medical Students.	Graduands.
1944	189	972	134
1945	339	1159	151
1946	649	1602	152
1947	600	1872	164
1948	465	1921	133
1949	356	1916	168
1950	321	1931	230
1951	320	1771	314
1952[1]	389	1657	293 (approx.)

[1] There is every indication that enrolments for 1953 will exceed 350.

It was expected that 1948 would have shown the peak of enrolments, after which the numbers would decline rapidly, as by then the majority of war service students coming in under the rehabilitation scheme would have enrolled. Since then, however, the number of Commonwealth scholarships, bursaries or other means of assisting students to enter the university as a whole have increased and the Faculty of Medicine still attracts large numbers, so it is likely that these large entries for the Faculty of Medicine will continue. This view is supported by Professor Copland, who, before he left for Canada early in February, 1953, pointed out that the student population in Australian universities prior to the war was 14,000, but increased rapidly to 30,000 when members of the forces were demobilized. The number had remained stable for the last two and a half years, but by 1955 an increase was expected to 32,000, by 1960 to 39,000, by 1965 to 47,500, and shortly after that to 50,000. If his forecast is anywhere near being correct there must be an increasing number of students entering the medical course, as on figures for 1952 about 13% of university students are in the faculties of medicine in our four universities, there being a total of 3771 medical students in 1952.

The Secretary of the Medical Board of New South Wales, Mr. P. E. Cosgrave, has supplied the information shown in Table II as to registrations of medical practitioners in this State, classified according to addresses given as at December 31, 1952.

A small proportion of those in New South Wales may have retired from active practice, but it is unlikely to exceed 1% as many men of advancing years say that they cannot afford to retire and live comfortably with the high rate of taxation which has developed since 1939. In fact many men who had retired have had to resume practice in recent years, and it is surprising to find a large number of doctors well over seventy years of age who are still in active practice.

In Table III the increasing number of doctors from Great Britain is not without interest, as is also the number of foreign doctors who have completed the three years at the University of Sydney which entitles them to registration for practice in New South Wales only. There were 50 attending the university in 1952. Of the eleven recommended to the Minister of Health for registration under special provisions of the *Medical Practitioners Act*, two were registered for research work, but the other nine with established reputations were recommended to the Minister for registration forthwith as having such special knowledge and experience as would justify waiving the usual requirements of the Act.

In the past seven years no less than 88 foreign doctors have been admitted to practice in New South Wales. The unusual influx from other Australian universities in the last two years is difficult to explain.

TABLE II.

Showing Location of Medical Practitioners on the New South Wales Register.

Group.	Number.
Registered and resident in New South Wales:	
City	645
Suburbs	2256 } 4034
Country	1133
Registered and resident in other States:	
Queensland	418
Victoria	345
Tasmania	75 } 996
Australian Capital Territory ..	31
South Australia	65
Western Australia	62
Registered and resident elsewhere[1] ..	464
Grand total on New South Wales register	5494

[1] This includes 314 in Great Britain, mainly post-graduate students.

Vital Statistics.

Since the Census was taken on June 30, 1947, the Commonwealth Immigration Scheme has come into operation and, excluding the balance of that year, the population of Australia, then given as 7,580,820, has been increased by approximately 667,548 permanent arrivals (that is, persons intending residence for one year or longer), but not all of these have been immigrants, as for instance in 1951 there were 132,542 permanent arrivals, of which 111,433 were immigrants.

TABLE III.

Year.	Registrations of Medical Practitioners in New South Wales.				
	Total.	From Great Britain.	Foreign.		From Other Australian Universities.
			Special.	Three Years University.	
1946 ..	181	10	0	9	1
1947 ..	200	16	1	23(*b*)	1
1948 ..	228	22	1	2	2(*c*)
1949 ..	93 (*a*)	25	4	0	3
1950 ..	232	25	1	14	1
1951 ..	304	44	3	7	23
1952 ..	400	42	1	22	26
Seven-year total ..	1638	184	11	77	57

(*a*) Only a few deferred examinees from the University of Sydney owing to change in curriculum.

(*b*) Twenty-two foreign doctors granted State registration for Commonwealth services in war years.

(*c*) One from New Zealand.

The Assistant Commonwealth Statistician has kindly supplied the following figures as at September 30, 1952: Australia (estimated population), 8,700,440; New South Wales (estimated population), 3,405,389.

The original target of 200,000 immigrants per year was never attained, the best year being 1950, when, according to figures in the daily Press, there were 174,540 permanent arrivals, but in 1951 the figures dropped to 132,542 and will probably be a little below that figure for 1952 (full figures not yet available). Last year the Commonwealth Government decided to cut its immigrant target to 80,000, so that

the estimated increase in the population of Australia to 10,700,000 by 1960 is not likely to be achieved. In the past seven years permanent arrivals have averaged a little over 100,000 *per annum*, and allowing for annual natural increase at the present rate of about 100,000 with an average of 50,000 permanent arrivals, the population of Australia by the end of 1959 would be approximately 9,750,000, of which some 4,000,000 would be in New South Wales.

The Proportion of Doctors to Population.

As was pointed out in 1948, it used to be thought that ten doctors per 10,000 of population (1:1000) was a fair working average, but in New South Wales the figure which had been about eight per 10,000, that is, one doctor for 1250 people, in previous years rose in 1948 to eleven per 10,000, or one doctor for every 909 of population. It was thought that with the extension of public health, repatriation, hospital and other social services an increasing number of medical men could be absorbed, and if one took a figure of 12·5 per 10,000 of population, or one doctor to 800, this should be a "reasonable estimate" to cover the next ten years. This figure has been quoted by the Minister for Immigration and by the Department of Labour and National Service as the "optimum figure" for Australia, but it does not apply in such a fashion, as New South Wales is a highly industrialized State with the major part of its population in and around Sydney, while several large country centres, such as Newcastle, Wollongong, Wagga, Goulburn, Maitland, Tamworth, Grafton, Lismore, Broken Hill *et cetera*, between them have a population of at least 400,000. The proportion of sickness and accident in big centres is higher than in the rural areas, and also such centres drain the surrounding regions as they have better hospital facilities and specialist services which are brought within the reach of people in outlying regions by improved methods of transport.

The Commonwealth Statistician gives the estimated population of New South Wales at September 30, 1952, as 3,405,389, which at one medical man per 800 people would require 4256 doctors, whereas on our register we had at that date about 4000, or one to 850 of population, that is, 11·7 per 10,000, which is very close to the figure of 11·2 for the Commonwealth as a whole which the Federal Council thought a reasonable figure.

The Supply of Doctors for the Future.

In 1948, when estimating the probable number of graduands from that year onwards, the very drastic figure was taken of 10% of sixth year students who would not graduate, although it was pointed out that students seldom retire from the medical course after their third year, but it was thought necessary to make an estimate well on the low side. With a normal increase in population and with the number of medical students enrolled it was estimated that 1951 would show that all doctors were absorbed at the ratio of one per 800 of population and that from 1952 onwards there would be a gradually increasing surplus. As things have turned out, there was not the big drop in first year enrolments that was expected, so that although the population of New South Wales is some 82,000 greater in 1952 than was estimated owing to the immigration influx, our new graduates with the advent of an increasing number of doctors from other States and Great Britain, foreign doctors being admitted for registration after completion of the last three years of the medical course and the few registered under special provisions of the *Medical Act*, have combined to supply the increase necessary to balance up with the increase of population.

The threatened overcrowding of the medical profession in New South Wales which was forecast to make itself felt from 1952 onwards has been delayed only, as it appears very likely that there will be a steady increase in the number of students enrolling in medicine as well as in other faculties and the increase in population will not be nearly as great as has occurred in the past five years.

One can therefore regard with concern what the next seven years have in store for the medical profession, even though the surplus of doctors may not be as great as was originally anticipated.

Reference to Table IV gives the actual position for the years 1949 to 1952 except that at the time of writing the Commonwealth Statistician could supply figures only up to September, 1952 (3,405,389), so the increase in the last quarter had to be estimated at 25,000. From 1953 to 1960, anticipating that the population of New South Wales would then reach four million, an average of 71,326 was struck, but this may be over-estimated for the first three or four years, after which the lag would be overtaken and there would be a corresponding difference in the balance of doctors for these years. But by 1960 there could be a surplus of 772 doctors which would mean a ratio of 1:692 of population, or 14·4 per 10,000, a figure exceeding the present one of the United States of America, which is about 14·0 per 10,000 and is regarded with disfavour as such overcrowding brings malpractice with it.

The numbers of graduands from the University of Sydney are based on official figures for 1949 to 1952, but it is to be noted that these new doctors do not come into the register until the following year, as although the university classes them as in the year of their final examinations and includes the deferred examination, their degrees are not conferred until some three months later in the following year, and

TABLE IV.

Year.	Estimated Population of New South Wales.	Doctors Required at Ratio of 1 to 800.	Total Registration in New South Wales.	New Graduands.	Balance.
1949 ..	3,175,935[1]	3,969	3,335[7]	168	−634
1950 ..	3,278,026[1]	4,097	3,495[7]	230	−602
1951 ..	3,358,760[1]	4,198	3,732[7]	314	−466
1952 ..	3,430,389[2]	4,288	4,056[7]	293	−232
1953 ..	3,501,715[3]	4,378[4]	4,349[8]	300[5]	−29
1954 ..	3,573,041	4,468	4,650	232[8]	+182
1955 ..	3,644,367	4,558	4,885	178[8]	+327
1956 ..	3,715,693	4,648	5,065	160[8]	+417
1957 ..	3,787,019	4,738	5,225	160[8]	+487
1958 ..	3,858,345	4,828	5,385	194[8]	+557
1959 ..	3,929,671	4,918	5,579	200[6]	+661
1960 ..	4,000,997	5,008	5,780	200[6]	+772

[1] As given by Commonwealth Statistician. [2] Estimated as final figures not available for the full year. [3] Estimated on an average addition of 71,326 annually to 1960. [4] Allowing an increase of 90 doctors annually for the increased population. [5] Estimated on basis of 50% of first year enrolments from 1947. [6] Estimated on increasing enrolments. [7] Actual figures. [8] Estimated.

it is not until then that they come on to the register. All new graduands do not register in New South Wales, but this loss along with deaths in the profession or removal of names from the register for other reasons is for practical purposes balanced by new doctors coming into this State from Great Britain or from other States. Thus in estimating total registrations for the State the number of new graduands has been added to the actual figure for that year and would thus provide the figure for the next year, for example, the actual registrations for 1950 were 3495, and if the 230 new graduands for that year are added it gives an approximation for 1951 of 3725, whereas actual registrations were 3732. The figures estimated in the 1948 article for probable registration proved to be somewhat on the high side, so the different method as explained above has been adopted as being more likely to be relatively accurate. This year may show a full absorption of doctors on the basis of 1 to 800 of population, but it appears that from 1954 on to 1960 we shall have a gradually increasing number of doctors competing with each other to earn a livelihood.

What of the Future?

Long-range forecasting can never be very accurate as so many factors may come into play, and we can only hope that another global war will not be forced on us.

Dr. Charles Byrne in THE MEDICAL JOURNAL OF AUSTRALIA, March 7, 1953, refers to many major changes that have occurred in recent years which have an important bearing on the medical profession, including the great upsurge in industry and the revolution in transport. Added to these are the increasing social services, public health development, construction of base hospitals, the widening scope of industrial medicine, the increase in the armed services *et cetera*. All of these give a gradually widening scope for the utilization of medical men, but it is doubtful whether we can drop much below a ratio of 1 per 800 of population, that is, 12·5 per 10,000.

In 1947 the figure for Great Britain was 9·5 per 10,000, while for the United States of America it was 14·0, and it is likely that both figures have altered materially for the worse. *The Lancet*, December 20, 1952, in an editorial, refers to the Collings report of 1950 as follows: "The overall state of general practice is bad and still deteriorating. The deterioration will continue until such time as the province and function of the general practitioner is clearly defined, objective standards of practice are established and steps taken to see that these standards are attained and maintained."

With the advent of the National Health Service in Great Britain the general deterioration has been accelerated and caused such concern that it has been a factor in the formation of a College of General Practitioners in an endeavour among other objectives to improve the position.

Again *The Lancet*, January 3, 1953, also in an editorial, refers to a recently published book by Roy Lewis and Angus Maude, "Professional People", which the reviewer states "is a masterly account of the present situation of professions in general and the dangers facing them". *The Lancet* states: "The danger, as Lewis and Maude see it, lies in a later lowering of standards when the State finds that it has undertaken to do more than it can pay for."

As regards the United States of America, references have been made in the lay Press by responsible leaders of the profession to the increasing frequency of unnecessary treatments both medical and surgical, ghost operators, fee splitting *et cetera*, resulting from an overcrowded medical profession, some members of which are resorting to such unethical means of securing an adequate income.

A further threat to the medical profession is the great increase in the ancillary services, many of which now employ technicians, laboratory workers, social workers *et cetera*, who are now forming their own unions or associations and are weakening the position of the qualified medical practitioner. Sir Heneage Ogilvie looks upon this tendency with foreboding. The medical profession in the past has condoned and encouraged such ancillary services, but steps may have to be taken to see that such services by lay workers do not usurp the functions of the doctor. The lay Press is running regular medical commentaries and giving gratuitous and often misleading advertisement to modern developments in medicine and surgery, so that the public are seeking medical advice more freely than they used to and are even demanding certain services, thus throwing an added burden on such hospital departments as hæmatology, biochemistry, radiology *et cetera*. Dr. Charles Byrne refers to the enormous accident rate of the roads since the advent of mechanical transport, and mentions the fact that on November 10, 1952, in four adult public hospitals in Melbourne nearly 9% of the beds occupied were by people injured in road accidents with an unrecorded number treated in casualty and out-patient departments. He also refers to the fact that the conquest of many epidemic and acute diseases has helped to increase the span of life so that there are more crippled or otherwise damaged and aging people requiring medical supervision. Also various stress diseases due to the increased *tempo* of life are on the increase, such as peptic ulceration, thyrotoxicosis, nervous disorders, arteriosclerosis *et cetera*, all of which increase the demand for medical services. With the modern advances in the methods and machinery for diagnosis and treatment there must be increasing specialization, and as such improvements are costly, they cannot be used by the profession as a whole other than through large and well-equipped metropolitan or base country hospitals which in turn must allow for an increasing number of specialists on their staffs. Such factors may allow of absorption of a small proportion of our threatened surplus of doctors, but there must be an ever-increasing demand on hospitals, many of which in suburban and country areas cannot yet provide the special equipment and specialist services now coming to be regarded as essential for the needs of the public. The larger metropolitan hospitals have increased their honorary specialist staffs, and in the base hospitals in the major country districts specialists in various branches of medicine are slowly coming on the staffs. In so many country and outer suburban hospitals the general practitioners have in the past carried on to the best of their abilities and feel they have vested rights so that men with specialist knowledge and training are sometimes resented and find it extremely difficult to establish themselves in the district so as to earn a living. Dr. T. Giblin in THE MEDICAL JOURNAL OF AUSTRALIA, March 21, 1953, refers to the problem of the general practitioner and specialist status in England under the National Medical Service where smaller country town hospitals now have visiting specialists appointed to the exclusion of the general practitioners. It is unlikely that such complete replacement of general practitioners will ever come about in this country, but it has to be realized that no one man can be an all-round specialist and that for their own protection an increasing number of general practitioners should aim towards directing their studies, interests and work along definite lines as can be done in a group practice without jealousy or fear of losing patients. Such considerations are mentioned as a possible means of absorbing some of the excess doctors whose advent is threatened within the coming decade.

HUGH R. G. POATE,
Sydney.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on December 5, 1952, at the Saint George Hospital, Kogarah, New South Wales. The meeting took the form of a series of clinical demonstrations by members of the medical and surgical staffs of the hospital.

Cavernous Sinus Thrombosis.

DR. J. C. ENGLISH presented a man who had been suffering from cavernous sinus thrombosis. The history was that the patient had had a "cold" for one week, and had developed double vision, severe frontal headache, numbness around the left eye and ptosis of the left eye. After admission to hospital the patient became lethargic and developed left central artery thrombosis and proptosis of both eyes. Taste sensation on the anterior part of the tongue was lost. His mental condition deteriorated, and he became restless and semi-delirious. He was given intensive chemotherapy with penicillin, chloramphenicol and large doses of heparin. He developed corneal ulceration of the right eye with trophic changes, and lost the sight of the eye. He then made a slow recovery, during which the right arm became paralysed. It was thought that the paralysis might have been hysterical.

Pyloric Stenosis Complicated by Alkalosis.

Dr. English also showed a man, aged forty-five years, who had been suffering from chronic duodenal ulcer and pyloric stenosis complicated by alkalosis. The patient had been admitted to hospital on October 7, 1952, suffering from tetany. He was given two doses, at half-hourly intervals by intravenous injection, each of 10 millilitres, of 10% calcium gluconate in 0·2N saline with dextrose. One gramme of ammonium chloride was given three times a day for three days. He was not vomiting, and was allowed to take fluids by mouth. The tetany was controlled. All treatment was then suspended, and in a few days his diet was increased, but he then commenced to vomit and his abdomen became distended. Treatment was recommenced with calcium gluconate, saline and ammonium chloride. Similar attacks occurred several times until October 30, always following attempts to increase the diet. On October 30, his hæmoglobin value was 69% (10·7 grammes *per centum*) and his blood urea content (non-fasting) was 164 milligrammes *per centum*. He was then given ammonium chloride, one gramme three times a day for three days. On the following day his blood urea content was 180 milligrammes *per centum*. The carbon dioxide combining power of the blood was 115 volumes of carbon dioxide *per centum*. The serum chloride content was 231 milligrammes *per centum*. The serum calcium content was 8·5 milligrammes *per centum*. The serum phosphorus content was 5·0 milligrammes *per centum*. The thymol turbidity test result was 2·4 units. The patient's general condition was improving, although his urine contained occasional red blood cells. By November 11 the blood urea content had dropped to 36 milligrammes *per centum*, and the carbon dioxide combining power to 78 volumes *per centum*. The serum chloride content had increased to 546 milligrammes *per centum*, and the serum protein content was 5·4 grammes *per centum*. The patient's condition was satisfactory, and it was decided to perform partial gastrectomy. On November 11, as a result of gastric washing and the removal of hydrochloric acid, the patient had another attack of tetany, which was controlled with saline and ammonium chloride. On November 13, partial gastrectomy was carried out with an anterior antiperistaltic anastomosis. The patient was found to have a chronic duodenal ulcer and pyloric stenosis. Subsequently, the patient received routine post-gastrectomy treatment with administration of vitamins *B* and *C* and of 100,000 units of penicillin, six-hourly. By November 23 he was gaining weight and convalescence was proceeding satisfactorily. Symptoms of tetany had not recurred.

Cystic Disease of the Lung.

DR. R. W. THOMPSON presented a man, aged forty-six years, who had first come for examination four weeks previously because of loss of weight (two stone in twelve months) and lassitude of nine months' duration. No other symptoms could be elicited. The patient was a butcher and had engaged in no mining or quarrying occupation. His mother had died of septicæmia at the age of fifty-four years. His father had died of pneumonia at the age of fifty-six years, but it was known that the father had been shown at

a clinic as "an interesting chest case", his condition being associated with pulmonary osteoarthropathy, but the actual diagnosis was unknown. His brothers were alive and well. He had arrived from England one year previously. He had suffered from pneumonia in 1946. A consulting physician at the Manchester Northern Hospital had given the following report in 1950: "The X-rays show a local emphysematous condition in the right apex with also localized pleural thickening at the apex. This man's clinical condition is excellent, and in my opinion, the X-ray abnormality is entirely oldstanding and of little or no significance—no evidence of tuberculosis." On examination, the patient was found to be a thin man of stated age and normal development. No obvious abnormality was present, except well-marked clubbing of the fingers. The breath sounds were diminished over the upper half of both lungs, with hyperresonance to percussion over the upper half of the right lung. No other clinical abnormality was found. Sputum and gastric concentration tests had not been performed. The radiologist reported the following X-ray findings: "On both sides, large cystic areas with thin, well defined septa are present in both lungs, mainly in the hilar regions and upper and middle zones. Much more marked on the right side. These are due to congenital cysts." Dr. Thompson said that a bronchogram confirmed those findings and revealed a grossly depressed bronchial tree distorting everything on the right side. The whole of the lower lobe of the right lung was incompletely filled. Very slight dilatation was present in the bronchi that contained the opaque medium.

Sturge-Weber Syndrome.

DR. G. C. WILSON presented a woman, aged nineteen years, suffering from a large angioma of the left fifth cranial nerve, which had been present at birth. She had glaucoma with cataract in the left eye. The angioma involved the palate and half the tongue and showed a tendency to spread to the opposite side. In infancy, the patient had had episodes of loss of consciousness, accompanied by general loss of tone, but not associated with convulsions. For several years she had been free from the seizures, which then recurred when she was aged ten years. They occurred about twice in a month, being more common at the time of menstruation. In them, the patient suddenly lost consciousness, turning the head to the right. She fell to the ground, but had no convulsions. Post-ictal confusion occurred, but no paresis was noted. She had occasional headaches. Her school work was always poor, but she could read and write. The family history was not known. Apart from the angioma and the eye changes, the cranial nerves were normal on examination. Dr. R. Hertzberg reported that the right eye was normal. The left eye had no vision—not even perception of light. The conjunctiva had been involved; the iris of the eye was less pigmented than that of the right eye, and some large vessels were seen on it. The pupil failed to react, and there was an opacity in the lens. The tension in the eye was 55 millimetres of mercury, a normal reading being 15 to 25 millimetres of mercury. Dr. Hertzberg said that the glaucoma was an integral part of the syndrome and was associated with angioma of the choroid. X-ray examination of the skull revealed no cortical calcification. Dr. Leonard Rail reported that the electroencephalographic record was abnormal, indicating a widespread lesion in the left parieto-occipital and temporo-occipital regions. It was quite consistent with an angioma occupying those regions. Radioactive iodofluorescein was injected intravenously, and the cortical deposition measured with a Geiger counter. That showed appreciably greater absorption on the right side than on the left, confirming the presence of a widespread lesion in the region of the left parieto-occipital and temporo-occipital regions. Discussing the patient's condition, Dr. Wilson said that the Sturge-Weber syndrome consisted of hæmangioma over the fifth cranial nerve region, with meningeal hæmangioma and congenital glaucoma. The cutaneous hæmangioma with the meningeal lesion constituted Krabbe's syndrome. The combination of cutaneous hæmangioma with glaucoma or choroidal angioma was also met with, but the combination of glaucoma with meningeal hæmangioma had not yet been described. It was noted that the conditions might all appear singly. The points to be noted were that the cutaneous hæmangioma varied in appearance and extent, and might be small and hidden by hair, or bilateral and involving large areas of the body surface. The size of the nævus was no indication of the amount of cerebral involvement. The cerebral component was an angioma of the pia and cortex. The dura was rarely involved. It was associated with superficial gliosis and atrophy of the underlying area of brain with corresponding nervous defect, most often parieto-occipital in position. Calcification of a characteristic appearance often accompanied the lesion. It was situated in the outer layers of the cortex, not in the angioma. Epilepsy and nervous defect appeared according to the area of damage. There were usually hemiplegia and hemianopia. Associated basal aneurysms were present sometimes. Usual investigations were X-ray examination of the skull, electroencephalography, arteriography, air studies, and intravenous injection of radioactive iodofluorescein followed by examination with the Geiger counter. X-ray examination of the skull might reveal calcification. Electroencephalography would show focal signs and the general extent of the lesion, and provide a serial check on progress. Arteriography did not show the meningeal angioma, but it might show associated aneurysms or cerebral angiomata if they were present. Air studies revealed dilated ventricles where extensive atrophy had occurred. Treatment was by means of anticonvulsive drugs, surgery and X-ray therapy. Suitable drugs were phenobarbitone, phemitone and "Dilantin". Surgical procedures were (*a*) excision of the affected area and (*b*) ligation of vessels in the meninges supplying the angioma. Dr. Wilson said that in the case under discussion, the patient's seizures had been controlled for three months with "Dilantin" and "Prominal", and it was considered that surgery was, for the time being, not indicated.

Narcolepsy and Cataplexy.

Dr. Wilson's second patient, a woman, aged twenty-three years, had had attacks of uncontrollable sleep over the past three years, occurring more frequently when she was tired. They might occur without warning or might be preceded by drowsiness and a desire to sleep. They occurred at various times and at various places—at the table, in buses and while she was talking to friends. She had also attacks of complete weakness, which were liable to occur with any emotion or shock, and especially when she was laughing or when her anger was roused. The frequency of both types of attacks had been increased in the past few months, during which time she had been more fatigued and more emotionally disturbed than previously. She had also suffered from particularly vivid dreams, which, Dr. Wilson pointed out, were said to be a frequent accompaniment of the disorder. On at least two occasions the emotion produced by the dreams had awakened her and had induced a cataplectic attack. She had also noticed a loss of power in one limb on occasions—for example, when excitedly chasing her children. She had developed a limp which subsided when she again became calm. She had had one infantile attack of convulsions. There was no history of head injury or encephalitis, nor was there any family history of importance. Physical examination of the patient and X-ray examination of her skull revealed no abnormality. Electroencephalography, carried out by Dr. Leonard Rail, showed no abnormality, though during the examination the patient fell asleep. "Drowsy" waves appeared, followed by a rhythm representing light sleep which ceased when she was awakened. Dr. Wilson said that the attacks had lessened in frequency since the patient had been treated with "Benzedrine" and "Dexedrine". Discussing the case, Dr. Wilson defined narcolepsy as a clinical syndrome characterized by brief, recurrent attacks of irresistible sleep, or of a condition which closely resembled sleep. The duration was a few seconds to a few minutes. Cataplexy consisted of sudden attacks in which, under the influence of emotion, especially laughter, the muscles became limp and powerless and the patient sank to the ground, unable to move or speak but fully conscious. Duration was about thirty seconds. There were many variations in the attacks, but the combination of the two types of attack formed a unique clinical feature. Each condition could be either primary or secondary. The cause of primary narcolepsy was unknown, but it was possibly related to the epilepsies. The age of onset was ten to forty years. Males were affected twice as often as females, and the condition tended to persist throughout life with remissions. Narcolepsy might be secondary to encephalitis or neoplasm. "Sleep attacks" might also occur in association with cerebral arteriosclerosis, syphilitic basal meningitis and, very rarely, trauma. In the differential diagnosis of narcolepsy, one had to consider hysterical or neurotic dissociation or sleep, and also prolonged *petit mal* due to idiopathic epilepsy (characterized by a three cycles per second wave and spike) and temporal lobe involvement (characterized by focal spikes and slow waves). Primary cataplexy was usually associated with narcolepsy; secondary cataplexy followed certain frontal lesions. In the differential diagnosis of cataplexy one had to consider akinetic epilepsy, myoclonic epilepsy of the type which projected the patient to the ground, and minor epilepsy with a minimal unconscious period. Neurosis and conversion hysteria were to

some extent simulated by the attack of loss of power, as in "a limb raised in anger fell limply to her side". Dr. Wilson said that the electroencephalogram in cases of primary narcolepsy and cataplexy was contradictory. In some cases an epileptic type of change was seen, in others the records resembled those of normal sleep. In the case under discussion, normal sleep waves were recorded during an attack. Treatment of the condition was by means of ephedrine and "Benzedrine".

Nephrotic State.

Dr. Wilson's third patient, a woman, aged thirty-six years, had come under observation in 1946 during the last two months of her second pregnancy, when she had œdema of the feet and ankles, hypertension and faint albuminuria. Surgical induction of labour was carried out; she had a post-partum hæmorrhage and required blood transfusion. It was found that she had had "kidney trouble" during the last month of her previous pregnancy five years earlier. She had then remained symptom-free till February, 1951, when she was admitted to hospital with headache, biliousness and general œdema. She had a raised blood pressure and severe albuminuria. The fasting blood urea content was increased to 28 milligrammes *per centum*. The urine contained numerous hyaline casts, organisms, pus cells and coliform bacilli. The total serum protein content was 6·1 grammes *per centum* and the urea concentration was 70% of normal. Treatment by means of salt restriction and a high protein diet brought gradual improvement. However, she had heavy albuminuria with recurring facial and dependent œdema until one year later when she was again admitted to hospital with gross œdema, ascites and oliguria. She was again found to be suffering from hypertension. The fasting blood urea content was 72 milligrammes *per centum* and the urea concentration was 84% of normal. Again the condition subsided with rest and diet. In May, 1952, gross generalized œdema and ascites returned. The ocular fundi were found to be œdematous, the blood pressure was increased to 210 millimetres of mercury, systolic, and 130 millimetres, diastolic, and the fasting blood urea content was 64 milligrammes *per centum*. The total serum protein content was 7·2 grammes *per centum*, made up of albumin 2·2 grammes and globulin 5·0 grammes, a ratio of 0·44 to 1·0. The serum cholesterol content was 1121 milligrammes *per centum*, a finding that was confirmed by repetition of the examination. The urine contained many hyaline casts, erythrocytes and leucocytes, but no organisms. In view of the gross œdema and absence of severe azotæmia, "Thiomerin" was given in an amount of one to three millilitres per week in divided doses. Again diuresis occurred with improvement in the patient's general condition. It was noted that at the time of admission to hospital, on that occasion the patient's weight was nine stone four pounds. In November, 1952, the patient felt well and œdema was minimal. Her weight was seven stone eleven pounds, her blood pressure was 180 millimetres of mercury, systolic, and 120 millimetres, diastolic. The serum cholesterol content was 615 milligrammes *per centum*. The total serum protein content was 5·5 grammes *per centum*, made up of 3·1 grammes of albumin and 2·4 grammes of globulin, a ratio of 1·3 to 1·0. The fasting blood urea content was 44 milligrammes *per centum*. The carbon dioxide combining power of the blood was 44·8 volumes *per centum*. Excretion pyelography revealed poor excretion. The blood sedimentation rate was 123 millimetres in one hour. Dr. Wilson commented that the fall in the total serum protein content, the high blood sedimentation rate and low carbon dioxide combining power, with the persistence of hypertension, were sobering features suggesting the onset of a terminal phase of the illness in spite of the quantitative increase in the serum albumin content and the complete absence of discomfort. It was considered that the patient's condition was probably type 2 nephritis with certain unusual features. Features indicating the nephrotic state or type 2 nephritis were the recurrent œdema and ascites, the massive albuminuria, the raised serum cholesterol content, and the reversed albumin-globulin ratio. Features of interest in the case were, firstly, the extremely high serum cholesterol content and, secondly, the return of the albumin-globulin ratio to nearly normal values from a critically low level of albumin in spite of a fall in the total serum protein content. It was not clear whether the occurrence was a natural remission or the result of diuresis induced by a mercurial diuretic. Further possible treatment included intravenous administration of serum albumin, the transfusion of whole blood, the intravenous administration of dextran, the administration of cortisone, the induction of malaria, and the use of Southey's tubes for œdema of the legs. Dr. Wilson said that the intravenous administration of serum albumin would need to be heroic, as patients in such cases might excrete 10 to 20 grammes of protein per day, as much as was contained in two or three litres of plasma. With regard to malaria, Dr. Wilson said that its induction had been described in *The Lancet* recently as providing an effective and easily controlled intercurrent infection, lessening œdema and inducing a remission in children.

(To be continued.)

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

AN OFFICER OF THE GOVERNMENT WRITES TO THE PRESS.[1]

Colonial Secretary's Office,
Sydney,
11th October, 1854.

The Medical Adviser to the Government.

Sir,

A letter having appeared in the Sydney Morning Herald of the 7th inst. signed by Mr. George Walker, Acting Medical Officer of the Lunatic Asylum at Tarban Creek, requesting the public to suspend their judgement with reference to certain papers which have been laid before the Legislative Council relative to the treatment of lunatics temporarily confined in Darlinghurst Gaol, I have the honour by direction of His Excellency the Governor-General to inform you that he is willing to believe that his letter was addressed by Mr. Walker to the Editor of the Sydney Morning Herald in ignorance of the rule of the Public Service which prohibits officers of the Government from appealing to the public or corresponding with the newspapers on matters connected with their official conduct or duties, and I have therefore to request that you will point out to Mr. Walker that if he does not strictly conform to it for the future it will be His Excellency's very painful duty to dismiss him from his office without further warning.

I have, etc.,

W. ELYARD.

Post-Graduate Work.

ANTI-CANCER COUNCIL OF VICTORIA.

THE Anti-Cancer Council of Victoria invites members of the medical profession to attend a series of four lectures on "Cancer Casualties in the State of Victoria", to be given by the staff of the Central Cancer Registry at the Royal Australasian College of Surgeons' Hall, Spring Street, Melbourne (by courtesy of the Royal Australasian College of Surgeons). The lectures will commence at 4.30 p.m., and the subjects and dates will be as follows:

Thursday, May 21: "Demography in General and Cancer Surveys in Particular."
Thursday, July 23: "Measurement of Combined Cancer Experience of Melbourne's Clinical Schools."
Tuesday, September 22: "Uterine Cancer Casualties: 1940-1950."
Thursday, November 26: "Bronchogenic Cancer Casualties: 1940-1950."

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Annual Subscription Course.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that, in conjunction with the Australian Orthopædic Association, New South Wales Branch, Professor Joseph S. Barr will give the following

[1] From the original in the Mitchell Library, Sydney.

lecture on Friday, June 5, 1953, in the Stawell Hall, 145 Macquarie Street, Sydney, at 8.15 p.m.: "Some Observations Concerning Low Back and Sciatic Pain." Professor Barr is Clinical Professor of Orthopædic Surgery at Harvard University Medical School, and Chief of Orthopædic Surgery, Massachusetts General Hospital, Boston, United States of America.

The Royal Australasian College of Physicians.

GRANTS FOR MEDICAL RESEARCH.

A COMMUNICATION has been received from The Royal Australasian College of Physicians reminding medical practitioners that funds are available for grants by the College for approved medical research. Application forms may be obtained from the Acting Honorary Secretary at the office of the College, 145 Macquarie Street, Sydney.

Correspondence.

BLOOD TRANSFUSION IN AUSTRALIA.

SIR: I am somewhat puzzled by the letter headed "Blood Transfusion in Australia" which appeared in your issue of April 25, 1953.

The Red Cross Blood Transfusion Service is not nationalized any more than the Flying Doctor Service, the Bush Children's Health Scheme, or the Queensland Ambulance Transport Brigade in this State—all of which receive government subsidies. I personally am opposed to any form of nationalization, just as I am also opposed to any other form of monopoly. The fact that an independent blood bank does exist in Queensland indicates that there is no monopoly in transfusion work in this State. After all, there is plenty of room for all types of service.

I personally regret the many inaccuracies which appear in the letter in question, and would be only too happy to supply accurate information concerning the costs of operation of this service to any who are interested.

Yours, etc.,

A. E. SHAW,
Divisional Director (Queensland),
Red Cross Blood Transfusion Service.

April 28, 1953.

MASS RADIOGRAPHY SURVEY.

SIR: In the issue of May 2, 1953, Dr. Rubinstein tells of the mass radiographic survey the Anti-Tuberculosis Association of New South Wales has commenced in Sydney. I am fully aware of the excellent work of the medical staff of the association and support his plea that all, young and old, should take advantage of chest X rays as offered by mobile units or for that matter fixed units at radiologists' rooms, hospitals *et cetera*.

Dr. Rubinstein seeks the cooperation of the profession in the survey. As one who gratefully acknowledges all assistance from Dr. Rubinstein and his associates both in private practice and clinics, I hope that his association will give the same cooperation to all the medical profession. It is generally agreed that when an abnormality is revealed by chest X ray needing further investigation, the patient should be given the opportunity of seeing his own doctor. If the latter is not anxious to continue with the investigation, then he will no doubt seek the help of others. Should the patient desire to attend a chest clinic, he should be given a list of clinics and be recommended to attend the clinic nearest his place of residence.

It is surprising that many of the profession are unaware of the chest clinics which have been established for many years at the Royal Prince Alfred Hospital, the Royal North Shore Hospital of Sydney, Sydney Hospital, Canterbury District Memorial Hospital, Manly Hospital, Saint George Hospital and the Eva Hordern Red Cross Home.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 11, 1953.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1(1)	4	..	..	..	..	..	..	5
Amœbiasis	..	1(1)	..	..	..	..	..	..	1
Ancylostomiasis	..	..	..	..	..	..	7	..	7
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	1(1)	..	..	..	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	2(2)	1(1)	4(2)	..	..	..	2	..	9
Diphtheria	18(15)	13(5)	6(2)	..	2(1)	..	..	..	39
Dysentery (Bacillary)	..	1(1)	..	2(2)	..	..	..	1	4
Encephalitis	..	1(1)	..	..	..	1(1)	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	..	6(2)	..	4(1)	..	..	..	..	10
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	4	..	..	..	..	..	4
Malaria	..	..	..	..	..	..	..	..	..
Meningococcal Infection	1(1)	2(2)	2	..	..	..	..	..	5
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	15(11)	16(5)	13(2)	6(4)	1(1)	1	..	..	52
Puerperal Fever	1	..	..	..	..	..	..	..	1
Rubella	..	21(15)	..	..	4	..	..	..	25
Salmonella Infection	..	..	..	..	2(2)	..	..	..	2
Scarlet Fever	11(8)	91(50)	5(1)	2	..	..	..	1	110
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	1	1	..	..	..	..	..	2
Trachoma	..	..	..	..	..	..	..	..	..
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	24(13)	40(28)	9(1)	2(1)	5(3)	5(1)	..	..	85
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	3(3)	..	..	..	3
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

In the fight against tuberculosis it is most desirable that all interested persons and bodies should help share the responsibility.

Yours, etc.,
G. BRUCE WHITE.

British Medical Association House,
135 Macquarie Street,
Sydney.
May 4, 1953.

A COLLEGE OF GENERAL PRACTITIONERS.

SIR: The College of General Practitioners is rapidly gaining support from general practitioners in Great Britain, and a branch of the College has been formed in Scotland with its headquarters in Edinburgh. To enable practitioners in other parts of the British Commonwealth to join the College, it has been decided to form Regional Faculties as forerunners to the formation of branches, in such places as the Australian States. Details of these Regional Faculties are published in the *British Medical Journal*, March 28, 1953.

At the annual post-graduate course of the Federation of Country Local Associations, held at Orange in March, 1953, I was given the opportunity to explain the objects of this new College. A keen interest was shown in the formation of this College, and I feel sure that it will receive considerable support from general practitioners in New South Wales. I would suggest that all those interested should enlist the support of their local medical associations to see that a Regional Faculty is formed in New South Wales.

Yours, etc.,
W. A. CONOLLY.

Main Street,
Cessnock,
New South Wales.
April 29, 1953.

Deaths.

THE following death has been announced:

MACKAY.—Charles Vincent MacKay, on April 26, 1953, at South Yarra, Victoria.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

O'Brien, Patrick Aloysius, L.R.C.P. (Edin.), 1950, L.R.C.S. (Edin.), 1950, L.R.F.P.S. (Glasgow), 1950, R.A.A.F. Station, Williamstown, New South Wales.

Coppleson, John Victor Malcolm, M.B., B.S., 1950 (Univ. Sydney), 43 Wunulla Road, Point Piper, New South Wales.

Maloney, Peter John, M.B., B.S., 1952 (Univ. Sydney), 32 Martin Road, Centennial Park, New South Wales.

Medical Appointments.

Dr. P. E. Bannon has been appointed government medical officer at Home Hill, Queensland.

Dr. Henry Erskine Downes has been appointed Acting Director-General of Health and Acting Director of Quarantine, Commonwealth Department of Health, during the absence from Australia of Dr. A. J. Metcalfe.

Dr. Gabriel Thomas Dadour has been appointed as a Quarantine Officer at Fremantle under the provisions of the *Quarantine Act*, 1908-1950.

Dr. R. Barnes and Dr. W. I. Seith have been appointed honorary medical officers at the Wallaroo Hospital, South Australia.

Professor R. H. Thorp and Dr. G. C. Smith, representing the University of Sydney, and Dr. A. W. Morrow, representing the British Medical Association, New South Wales Branch, have been appointed members of the Poisons Advisory Committee of New South Wales.

Dr. H. G. Wallace and Dr. C. J. Cummins have been appointed ex-officio members of the Poisons Advisory Committee of New South Wales.

Australian Medical Board Proceedings.

TASMANIA.

THE following have been registered, pursuant to the provisions of the *Medical Act*, 1918, as duly qualified medical practitioners: O'Brien, Joyce Margaret, M.B., B.S., 1949 (Univ. Melbourne); Phillips, William John Elliott, M.B., B.Ch., 1937 (Univ. Cambridge), M.R.C.S., L.R.C.P., 1936, M.R.C.P. (London), 1947, M.R.A.C.P., 1949.

Diary for the Month.

MAY 18.—Victorian Branch, B.M.A.: Finance Sub-Committee.
MAY 19.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 20.—Western Australian Branch, B.M.A.: General Meeting.
MAY 21.—Victorian Branch, B.M.A.: Executive of Branch Council.
MAY 21.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 26.—New South Wales Branch, B.M.A.: Ethics Committee.
MAY 27.—Victorian Branch, B.M.A.: Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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